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Abstract

Clinical effectiveness and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomised controlled trials within a comprehensive cohort study – results from the PROSPECT Study

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Background: The use of mesh in prolapse surgery is controversial, leading to a number of enquiries into its safety and efficacy.

Objective: To compare synthetic non-absorbable mesh inlay, biological graft and mesh kit with a standard repair in terms of clinical effectiveness, adverse effects, quality of life (QoL), costs and cost-effectiveness.

Design: Two randomised controlled trials within a comprehensive cohort (CC) study. Allocation was by a remote web-based randomisation system in a 1 :1 : 1 ratio (Primary trial) or 1 : 1 : 2 ratio (Secondary trial), and was minimised on age, type of prolapse repair planned, need for a concomitant continence procedure, need for a concomitant upper vaginal prolapse procedure and surgeon. Participants and outcome assessors were blinded to randomisation; participants were unblinded if they requested the information. Surgeons were not blinded to allocated procedure.

Setting: Thirty-five UK hospitals.

Participants: *Primary study*: 2474 women in the analysis (including 1348 randomised) having primary anterior or posterior prolapse surgery. *Secondary study*: 398 in the analysis (including 154 randomised) having repeat anterior or posterior prolapse surgery. *CC3*: 215 women having either uterine or vault prolapse repair.

Interventions: Anterior or posterior repair alone, or with mesh inlay, biological graft or mesh kit.

Main outcome measures: Prolapse symptoms [Pelvic Organ Prolapse Symptom Score (POP-SS)]; prolapse-specific QoL; cost-effectiveness [incremental cost per quality-adjusted life-year (QALY)].

Results: *Primary trials*: adjusting for baseline and minimisation covariates, mean POP-SS was similar for each comparison {standard 5.4 [standard deviation (SD) 5.5] vs. mesh 5.5 (SD 5.1), mean difference (MD) 0.00, 95% confidence interval (CI) –0.70 to 0.71; standard 5.5 (SD 5.6) vs. graft 5.6 (SD 5.6), MD –0.15, 95% CI –0.93 to 0.63}. Serious non-mesh adverse effects rates were similar between the groups in year 1 [standard 7.2% vs. mesh 7.8%, risk ratio (RR) 1.08, 95% CI 0.68 to 1.72; standard 6.3% vs. graft 9.8%, RR 1.57, 95% CI 0.95 to 2.59]. There were no statistically significant differences between groups in any other outcome measure. The cumulative mesh complication rates over 2 years were 2 of 430 (0.5%) for standard repair (trial 1), 46 of 435 (10.6%) for mesh inlay and 2 of 368 (0.5%) for biological graft. The CC findings were comparable. Incremental costs were £363 (95% CI –£32 to £758) and £565 (95% CI £180 to £950) for mesh and graft vs. standard, respectively. Incremental QALYs were 0.071 (95% CI –0.004 to 0.145) and 0.039 (95% CI –0.041 to 0.120) for mesh and graft vs. standard, respectively. A Markov decision model extrapolating trial results over 5 years showed standard repair had the highest probability of cost-effectiveness, but results were surrounded by considerable uncertainty. *Secondary trials*: there were no statistically significant differences between the randomised groups in any outcome measure, but the sample size was too small to be conclusive. The cumulative mesh complication rates over 2 years were 7 of 52 (13.5%) for mesh inlay and 4 of 46 (8.7%) for mesh kit, with no mesh exposures for standard repair.

Conclusions: In women who were having primary repairs, there was evidence of no benefit from the use of mesh inlay or biological graft compared with standard repair in terms of efficacy, QoL or adverse effects (other than mesh complications) in the short term. The Secondary trials were too small to provide conclusive results.

Limitations: Women in the Primary trials included some with a previous repair in another compartment. Follow-up is vital to identify any long-term potential benefits and serious adverse effects.

Future work: Long-term follow-up to at least 6 years after surgery is ongoing to identify recurrence rates, need for further prolapse surgery, adverse effects and cost-effectiveness.

Trial registration: Current Controlled Trials ISRCTN60695184.

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Glossary

General

Effect size

For all negative *continuous* outcomes For example, the Pelvic Organ Prolapse Symptom Score. A positive effect size (mean difference) of > 0 favours standard repair.

For all positive *continuous* outcomes For example, the EuroQol-5 Dimensions. A positive effect size (mean difference) of > 0 favours synthetic/biological/mesh kit.

For all negative *dichotomous* outcomes An effect size (risk ratio) of > 1 favours standard repair.

For all positive *dichotomous* outcomes An effect size (risk ratio) of > 1 favours synthetic/biological/mesh kit.

Readmission Related to prolapse surgery (for complications). Readmission for new prolapse, incontinence or mesh complications surgery presented separately.

Serious Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

Satisfaction with surgery

How is prolapse compared with before surgery? Very much better = cured (1); much or a little better (or very much better) = improved or cured (< 4); no change or worse = failed (> 3).

Satisfied with results of operation? Completely satisfied = cured (1); fairly satisfied = improved or cured (1 or 2); fairly or very dissatisfied = failed (3 or 4); not sure = separate category (5).

Symptoms

Prolapse

'Any' symptom Pelvic Organ Prolapse Symptom Score Symptom reported as 'occasionally or more often'.

'Frequent' symptom Pelvic Organ Prolapse Symptom Score Symptom reported as 'most or all of the time'.

Pelvic Organ Prolapse Symptom Score Range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time. Primary clinical outcome.

Prolapse-related quality of life 'Overall, how much do prolapse symptoms interfere with everyday life?' Using a visual analogue scale, score range from 0 (not at all) to 10 (a great deal). Primary quality-of-life outcome.

Symptomatic prolapse At least one prolapse symptom (Pelvic Organ Prolapse Symptom Score of > 0).

Individual prolapse symptoms

Abdo. any 'A heaviness or dragging feeling in your lower abdomen (tummy)?' Any = occasionally or more.

Abdo. freq. Frequent = most or all of the time.

Back any 'A heaviness or dragging feeling in your lower back?' Any = occasionally or more.

Back freq. Frequent = most or all of the time.

Blad. not empty any 'A feeling that your bladder has not emptied completely?' Any = occasionally or more.

Blad. not empty freq. Frequent = most or all of the time.

Bowel not empty any 'A feeling that your bowel has not emptied completely?' Any = occasionally or more.

Bowel not empty freq. Frequent = most or all of the time.

Pain any 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more).

Pain freq. Frequent = most or all of the time.

SCD any 'A feeling of something coming down from or in your vagina?' (any = occasionally or more).

SCD freq. Frequent = most or all of the time.

Strain blad. any 'A need to strain (push) to empty your bladder?' (any = occasionally or more).

Strain blad. freq. Frequent = most or all of the time.

Actions necessitated by prolapse symptoms

Digital evacuation of bowel Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time).

Extra hygiene measures Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time).

Fingers to ease discomfort Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time).

Fingers to help empty bladder Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time).

Fingers to help empty bowel Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

Objective prolapse (on examination) Stage 2b, 3 or 4, defined as leading edge beyond the hymen (> 0 cm) when POP-Q data are available.

Urinary

Any incontinence Defined as 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount).

Incontinence-related quality-of-life score 'Overall, how much does leaking urine interfere with your everyday life?' Using a visual analogue scale, score range from 0 (not at all) to 10 (a great deal).

International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score Sum of responses to above three questions. Range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10).

Overactive bladder Nocturia twice or more; *and* urinary urgency 'most or all of the time'; *and* urinary frequency nine or more times per day.

Severe urinary incontinence International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21.

Stress urinary incontinence 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time).

Urgency urinary incontinence 'Does urine leak before you can get to the toilet?' (most or all of the time).

Bowel

Active faecal incontinence Any faecal incontinence when bowel urgency 'most or all of the time' is also reported.

Bowel symptoms QoL score 'Overall, how much do bowel symptoms interfere with your everyday life?' Measured using a visual analogue scale: score range from 0 (not at all) to 10 (a great deal). This could be due to any one or a combination of the above bowel symptoms.

Bowel urgency 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time).

Constipation (ROME criteria, adapted) Any two of the following: stool passing once a week or less; straining most or all of the time; hard stools; bowel not feeling empty most or all of the time; manual manoeuvre to empty bowel most or all of the time.

Faecal incontinence (any/severe) Faecal incontinence of solid or liquid stool: 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time).

Passive faecal incontinence Any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

Vaginal and sexual

Dyspareunia (any, severe) Pain during sexual intercourse (any = a little or somewhat; severe = a lot).

Dyspareunia at baseline Denominator includes number of women who were sexually active and those who did not have a sex life because of prolapse symptoms.

International Consultation on Incontinence Questionnaire-Vaginal Symptoms score Combination of responses to vaginal symptom questions.

Sex life quality of life 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' Measured using a visual analogue scale: score range from 0 (not at all) to 10 (a great deal).

Vagina too tight 'Do you feel that your vagina is too tight?' (most or all of the time).

Vaginal symptoms QoL score 'Overall, how much do your vaginal symptoms interfere with your everyday life?' Measured using a visual analogue scale; score range from 0 (not at all) to 10 (a great deal).

List of abbreviations

AE	adverse event
Akaike	information criterion
BMI	body mass index
BNF	*British National Formulary*
CC	comprehensive cohort
CEAC	cost-effectiveness acceptability curve
CHaRT	Centre for Healthcare Randomised Trials
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DMC	Data Monitoring Committee
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions (3-level version)
FI	faecal incontinence
GLM	general linear regression model
GP	general practitioner
HES	Health Episode Statistics
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICI	International Consultation on Incontinence
ICIQ	International Consultation on Incontinence Questionnaire
ICIQ-FLUTS	International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
ICIQ-VS	International Consultation on Incontinence Questionnaire-Vaginal Symptoms
ICS	International Continence Society
IP	Interventional Procedures
IPAC	Interventional Procedures Advisory Committee
ISD	Information Services Division
IUGA	International Urogynecological Association
MD	mean difference
MI	multiple imputation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	net monetary benefit
OLS	ordinary least squares
OR	odds ratio
PFMT	pelvic floor muscle training
PIL	patient information leaflet
PMG	Project Management Group
POP-Q	Pelvic Organ Prolapse Quantification
POP-SS	Pelvic Organ Prolapse Symptom Score
PROSPECT	PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials
PSSRU	Personal and Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RO	recruitment officer
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

SE	standard error	UI	urinary incontinence
TSC	Trial Steering Committee	UTI	urinary tract infection
TVL	total vaginal length	VAS	visual analogue scale
TVT	tension-free vaginal tape	WTP	willingness to pay

Plain English summary

About 10% of women have pelvic organ prolapse surgery, and one-third require a further operation. To improve prolapse repair results, surgeons used synthetic mesh and graft materials to reinforce the repair because this had worked well for hernia repairs. This study aimed to provide evidence on whether or not the use of these materials are more effective than a standard/traditional repair.

We compared a standard repair with a standard repair supported with a synthetic non-absorbable mesh inlay or mesh inserted using a kit, or a semi-absorbable biological graft inlay. We asked women about their prolapse and other symptoms, assessed their prolapse measurements and compared the results between the different procedures.

Most women reported that their prolapse symptoms and quality of life improved after surgery. We found that all of the surgical options worked equally well, but mesh or graft surgery was more expensive. Adverse effects were similar in all groups, but some women who had synthetic mesh (around 1 in 20) needed extra surgery, typically to remove a small portion of the mesh. The need for further prolapse surgery was similar for all groups. Results in non-randomised women were similar to randomised women, suggesting that the overall results would apply to most UK women who are having prolapse surgery.

Overall, we found no benefit to women who were having mesh or graft material in the first 2 years, and the costs were higher. Some women did require additional minor surgery for synthetic mesh exposure. Participants will be followed up for at least 6 years after surgery to determine longer-term costs and consequences.

Scientific summary

Background

The treatment of women with pelvic organ prolapse is a considerable burden to the UK NHS. Prolapse is a progressive condition, often caused by childbirth, but symptoms appear many years later. Conservative treatment with pelvic floor exercises, oestrogens and pessaries might help in the earlier stages but 10% of women will require surgery, which has a high failure rate: 3 out of 10 women require further surgery. Surgeons and researchers have suggested that mesh or graft reinforcement of the repair might provide a better chance of cure and prevent the need for more surgery. This is important because if the failure rate is reduced, women will be exposed to less risk and the costs may be less to the NHS. However, there is growing concern about the long-term consequences of augmentation with foreign material.

Aims and objectives

The PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials (PROSPECT) study comprises a panel of pragmatic, parallel-group randomised controlled trials (RCTs) set within a comprehensive cohort (CC) design. The aim was primarily to compare the clinical effectiveness and cost-effectiveness of three treatment modalities [(1) synthetic non-absorbable mesh inlay; (2) biological graft; and (3) mesh kit using similar material] compared with a standard repair in women with pelvic organ prolapse of the anterior or posterior vaginal walls.

Primary outcome measures were women's symptoms measured using the Pelvic Organ Prolapse Symptom Score (POP-SS) and prolapse-specific quality-of-life (QoL) visual analogue scale. Cost-effectiveness was assessed as cost per quality-adjusted life-year (QALY) gained, based on the EuroQol-5 Dimensions (3-level version).

Secondary objectives were to compare the three treatments in terms of bladder, bowel and sexual function, adverse effects, objective measurement of anatomical prolapse stage [using the Pelvic Organ Prolapse Quantification (POP-Q) system], further treatment, cost to the health service and patients, and satisfaction with treatment. Longer-term implications for cost-effectiveness were explored using a Markov probabilistic decision-analytic model from the perspective of the NHS.

Methods

A total of 3087 women who were having prolapse surgery in 35 UK centres were consented between January 2010 and August 2013. Women who had anterior and/or posterior prolapse, and who were willing to be randomised, were eligible for one of two trials: the Primary trial (RCT1) for women who had de novo prolapse in one or both compartments, and the Secondary trial (RCT2) for those who had had at least one previous repair in the prolapsed compartment. Women who did not wish to be randomised, or who were advised by their surgeons to avoid randomisation, were followed up in matching observational CCs: primary women in CC1, secondary in CC2 and those with a uterine or vault prolapse alone in CC3.

Research ethics approval and fully informed consent were obtained. We included women who were deemed to require surgery based on symptoms and/or anatomical findings. We excluded women who were unable or unwilling to consent or unable to complete study questionnaires.

Study set-up

Women in RCT1 were randomised within three strata: stratum 1A included women who were randomised to one of all of the three treatment options – standard repair, mesh inlay and biological graft; stratum 1B compared standard repair with mesh inlay; and stratum 1C standard repair with biological graft inlay. In RCT2, women were randomised to one of three treatment options: stratum 2A (standard repair, mesh inlay and mesh kit); stratum 2B, comparing standard repair with mesh inlay; and stratum 2D, comparing standard repair with mesh kit.

Randomisation

Randomisation involved a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. Participants were randomly allocated 1 : 1 : 1 to one of the arms in the stratum for which they were eligible in the Primary trial, and 1 : 1 : 2 in the Secondary trial. The minimisation algorithm included surgeon, age (< 60 years or ≥ 60 years), type of planned prolapse repair (anterior, posterior or both), planned concomitant continence surgery and planned concomitant upper compartment prolapse repair. Women in the CCs received the surgery that they and their gynaecologist thought was most acceptable and suitable.

Study interventions

Surgeons were asked to use the surgical techniques with which they were most familiar. They informed us of their normal use of mesh and graft materials and details of their surgical techniques, but, as this was a pragmatic trial, deviation could occur both from the randomised allocation and their normal practice for clinical reasons. We recorded details of concomitant surgery for uterine or vault prolapse, continence surgery and the use of mesh.

Statistical analysis

An intention-to-treat analysis was performed. Primary and secondary outcomes were compared using generalised linear mixed models, adjusting for baseline covariates. Trial-based cost-effectiveness analysis assessed mean differences (MDs) in costs and QALYs at 1 year and 2 years. Estimates of cost-effectiveness were extrapolated to 5 years using a probabilistic Markov decision-analytic model. Estimates of cost-effectiveness were expressed as incremental costs per QALY gained, and the net monetary benefit approach was used to identify the optimal treatment modality on grounds of cost-effectiveness, based on a ceiling willingness to pay of £30,000 per QALY gained.

Results

In total, 3744 women waiting for prolapse surgery were screened for eligibility, of whom 3089 (83%) consented to participate in PROSPECT. Five of the 1507 (0.3%) who agreed to be randomised were excluded after randomisation. Of those included, 1348 were randomised in RCT1, with 1126 enrolled in CC1. Another 154 having a repeat repair were randomised in RCT2, with 244 in CC2. Finally, 215 women who were having either uterine or vault prolapse repair enrolled in CC3. The main reason for declining randomisation was the woman's or the surgeon's preference for a specific treatment. The majority (1264, 84%) of those randomised received their allocated treatment, 218 (15%) received a study treatment other than that randomised and 25 (2%) did not receive any of the study treatments. The 12-month follow-up appointment was well attended (1299, 86% of those randomised attended) and 1368 randomised participants (91%) completed the 12-month questionnaires (primary outcome).

Primary trials

Prolapse symptoms reported by women

The primary outcome was women's report of prolapse symptoms on the Pelvic Organ Prolapse Symptom Scale (score range 0–28) at 12 months after surgery. Adjusting for baseline scores and minimisation covariates, the mean POP-SS was similar for each comparison [trial 1: standard 5.4 vs. mesh 5.5; MD 0.00,

95% confidence interval (CI) –0.70 to 0.71; trial 2: standard 5.5 vs. graft 5.6; MD –0.15, 95% CI –0.93 to 0.63]. There was also no statistically significant difference in the prolapse-related QoL score (range 0–10) measured as the interference of prolapse symptoms with everyday life (trial 1: standard 2.0 vs. mesh 2.2; MD 0.13, 95% CI –0.25 to 0.51; trial 2: standard 2.2 vs. graft 2.4; MD 0.13, 95% CI –0.30 to 0.56).

Adverse effects

The number of women with serious non-mesh adverse effects, such as infection, pain, urinary retention and dyspareunia, was similar between the groups in the first year [standard 7.2% vs. mesh 7.8%; risk ratio (RR) 1.08, 95% CI 0.68 to 1.72; standard 6.3% vs. graft 9.8%; RR 1.57, 95% CI 0.95 to 2.59]. There were no statistically significant differences between the randomised groups for any adverse effect measure at any time period. The cumulative mesh complication rates over 2 years were 2 of 430 (0.5%) for standard repair (trial 1), 46 of 435 (10.6%) for mesh inlay and 2 of 368 (0.5%) for biological graft. The findings from CC1 were comparable.

Mesh complications in the Primary trials

In the first year, 2 of 430 women in the standard group and 32 of 435 in the mesh inlay group had mesh complications, with a further 2 out 368 mesh complications in the biological group. One woman in the standard group received mesh for her prolapse repair and had subsequent mesh exposure; the other had mesh exposure resulting from a concomitant procedure. Both women in the standard group, and 23 in the mesh inlay group, had surgery to remove or overlay the mesh [of whom 18 (72%) were asymptomatic and 16 (64%) had exposures of < 1 cm^2]. In the second year, 1 of 430 in the standard group and 25 of 435 in the mesh inlay group had a mesh complication (a repeat occurrence in 1 and 11 women, respectively). Of these, 17 in the mesh inlay group required surgical correction of the exposure [of whom 13 (76%) were asymptomatic and 10 (59%) had exposures of < 1 cm^2]. The remaining women received conservative treatment (such as mesh trimming in outpatients, oestrogen treatment or cautery with silver nitrate) or no treatment.

Economic outcomes

Both mesh repairs were more costly to perform, driven by the material cost of mesh. There was no evidence of differences in follow-up use of health services at 2 years. Synthetic mesh inlay was £363 more costly (95% CI –£32 to £758). Biological graft was significantly more costly (+£565) than standard repair (95% CI £180 to £950). The participant and wider societal costs added 40% to the total NHS costs across the treatment groups for all women, although there were no differences across treatment groups. Synthetic mesh had, on average, 0.071 additional QALYs (95% CI –0.004 to 0.145) relative to standard repair, whereas biological graft had, on average, 0.039 (95% CI –0.041 to 0.120). There was substantial uncertainty regarding the most cost-effective treatment strategy. None of the treatment strategies demonstrated a probability of being the most cost-effective strategy of $> 84\%$ (if society was willing to pay £30,000 for a QALY gained). Uncertainty remained across the range of sensitivity analyses undertaken.

A decision-analytic model to extrapolate results of RCT1 over a longer time shows that at 5 years there is no evidence that either mesh strategy would be a cost-effective use of NHS resources. Standard repair was, on average, the most cost-effective because of lower intervention costs, lower costs of treating mesh-related complications and similar rates of surgical failure at 2 years. However, further long-term follow-up is required to validate the extrapolation models used.

Secondary and clinical outcomes in the Primary trials

There were no statistically significant differences in any of the measures of bladder, bowel or sexual function in any of the randomised groups. There were no statistically significant differences in the number of women with residual prolapse beyond the hymen (objective measurement of anatomical cure of prolapse using the POP-Q system) (trial 1: standard 13.9% vs. mesh inlay 16.1%; RR 1.12, 95% CI 0.79 to 1.60; trial 2: standard 15.5% vs. graft 18.1%; RR 1.14, 95% CI 0.80 to 1.62).

Secondary trials

Prolapse symptoms reported by women

The primary outcome was prolapse symptoms (POP-SS, range 0–28) at 12 months after surgery. Adjusting for baseline scores and minimisation covariates, the mean POP-SS was similar for each comparison {trial 3: standard 6.6 [standard deviation (SD) 6.0] vs. mesh 6.1 (SD 6.4); MD –0.41, 95% CI –2.92 to 2.11; trial 4: standard 6.6 (SD 5.5) vs. mesh kit 5.9 (SD 5.3); MD –1.21, 95% CI –4.13 to 1.72}. There was also no statistically significant difference in the prolapse-related QoL score (range 0–10) measured as the interference of prolapse symptoms with everyday life (trial 3: standard 2.5 vs. mesh inlay 3.0; MD 0.43, 95% CI–0.90 to 1.75; trial 4: standard 2.0 vs. mesh kit 2.3; MD –0.31, 95% CI –1.99 to 1.36).

Adverse effects

The number of women with serious non-mesh adverse effects was similar between the groups in the first year (trial 3: standard 7/55, 12.7% vs. mesh inlay 5/52, 9.6%; RR 1.05, 95% CI 0.66 to 1.68; trial 4: standard 3/25, 12.0% vs. mesh kit 3/46, 6.5%; RR 0.49, 95% CI 0.11 to 2.16). The cumulative mesh complication rates over 2 years were 7 of 52 (13.5%) for mesh inlay and 4 of 46 (8.7%) for mesh kit, with no mesh exposures after standard repair. There were no statistically significant differences between the randomised groups in any other outcome measure at any time. The findings from CC2 were comparable.

Mesh complications in the Secondary trials

In the first year, none of the women in the standard group, 6 of 52 in the mesh inlay group and 3 of 46 in the mesh kit group had a mesh complication. Three women in the mesh inlay group and one in the mesh kit group had surgery to remove or overlay the mesh. In the second year, none of the women in the standard group, 2 of 52 in the mesh inlay group and 2 of 46 in the mesh kit group had a mesh complication. Of these, one woman in the mesh inlay and one in the mesh kit group required surgical correction. In total, six women required mesh surgery in the 2 years of follow-up. A further six women received conservative treatment and the rest required no treatment.

Economic outcomes

The additional cost of providing mesh inlay and mesh kits for women who were having a secondary prolapse repair were £398 (95% CI –£197 to £993) and £914 (95% CI £349 to £1478), respectively. At 2 years, synthetic mesh inlay was, on average, £238 more costly than standard repair (95% CI –£929 to £1405) and mesh kits were £873 more costly (95% CI –£27 to £1774). Incremental QALYs relative to standard repair were 0.018 (95% CI –0.149 to 0.185 QALYs) and 0.096 (95% CI –0.081 to 0.274 QALYs) for synthetic mesh and mesh kits, respectively. Owing to small sample sizes for the Secondary trial, there was not enough evidence to determine the most cost-effective treatment strategy.

Secondary and clinical outcomes in the Secondary trials

There were no statistically significant differences in the number of women with residual prolapse beyond the hymen (standard 14.0% vs. mesh inlay 14.0%; RR 0.59, 95% CI 0.18 to 1.92; standard 16.7% vs. mesh kit 0%). There were also no statistically significant differences in any of the measures of bladder, bowel or sexual function, but the sample size was too small to be conclusive.

Conclusions

There was evidence of no benefit from the use of mesh inlay or biological graft compared with standard repair in terms of efficacy, QoL, adverse effects (other than mesh complications) or any other outcome in women who were having a primary repair in the first 2 years. In those randomised to synthetic mesh in the Primary trial, the cumulative incidence of mesh complications was 10.6% over 2 years. Some women required surgery for mesh exposure but the majority were asymptomatic or had small exposures.

Unless there is a significant decrease in reoperation rates for failure in the medium or long term, it is unlikely that any type of mesh or graft would be cost-effective, given the excess cost over standard repair and the excess cost of treatments for mesh complications.

The sample size in the Secondary trial comparisons was too small to be conclusive.

Recommendations for future research

Long-term follow-up to at least 6 years after surgery is ongoing to identify the recurrence rates, need for further prolapse surgery and adverse effects.

Trial registration

This trial is registered as ISRCTN60695184.

Funding

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Chapter 1 Introduction

The PROSPECT Study (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials)

In 2009, the UK government National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme funded the PROSPECT Study. This monograph describes the research.

PROSPECT was a major multicentre UK randomised controlled trial (RCT) investigating the effectiveness (including safety) and cost-effectiveness of surgical treatment, primarily in terms of improvement in prolapse symptoms, in women who were having a primary or a secondary prolapse repair.

Description of the underlying health problem

Pelvic organ prolapse is the descent from its normal anatomical position of one or more of the female genital organs. Pelvic organ prolapse is caused by herniation through deficient pelvic fascia or due to weaknesses or deficiencies in the ligaments or muscles that should support the pelvic organs. There is little epidemiological research into this condition because it has a variety of presentations and they do not all cause symptoms, particularly in the early stages.[1] Commonly reported symptoms include a feeling of dragging or heaviness in the vagina, uncomfortable bulge distending the introitus, urinary symptoms (urgency and voiding difficulty), bowel symptoms, such as incomplete emptying, and sexual dysfunction.

Prevalence and natural history

Estimates of the prevalence of prolapse vary from 41% to 50% of women aged > 40 years.[2,3]

It has been estimated that women have a lifetime risk of 11% of undergoing surgery for urinary incontinence (UI) or prolapse and 7% for prolapse alone.[4] The annual incidence of surgery for pelvic organ prolapse is within the range of 15–49 cases per 10,000 women-years, and it is likely to double in the next 30 years.[1,5] Little is known about the prevalence and effectiveness of different types of operations but they are notoriously prone to failure: around 30% of women undergo further operations; the mean time interval between the first and a subsequent procedure is about 12 years, and the time interval between subsequent procedures decreases with each successive repair.[4]

Gynaecologists have recognised for some time that both anatomical failure of supporting pelvic structures and recurrence of prolapse after surgery are common. More recently, it has also been recognised that surgery can be followed by a greater impairment of quality of life (QoL) than the original prolapse itself (e.g. new UI after surgery). In addition, repair of one type of prolapse may predispose the women to the development of a different type of prolapse (a new or de novo prolapse) in another compartment of the vagina due to alteration in the dynamic forces within the pelvis.[4]

Significance in terms of ill health and use of NHS resources

Surgery is common. In England and Wales in 2004–5, 26,947 women were admitted to hospital with a main diagnosis of female genital prolapse, and 28,297 operations were performed (some women had more than one type of prolapse operation).[6] The majority of the operations (93%) were undertaken in women who were having anterior repair ($n = 8560$), posterior repair ($n = 5406$) or both operations

($n = 5654$), or with a concomitant uterine prolapse ($n = 6837$). Only 7% were in women with vault prolapse ($n = 1840$). Assuming a population of about 20 million women in the age group at risk for prolapse surgery (50–85 years), the UK operation rate is currently around 14–16 women who were having prolapse operations per 10,000 per year.[6,7]

The need is likely to increase because of the rising number of elderly women. It has been projected that the number of women in the age group 50–85 years (those most likely to need prolapse surgery) will increase by 1.44 million between 2012 and 2020.[6]

Description of standard management

Women with prolapse may be managed conservatively with pelvic floor muscle training (PFMT) and pessaries, or with surgery. In addition they require management of associated conditions, for example lower urinary tract symptoms, such as UI or overactive bladder syndrome; bowel problems, such as constipation or faecal incontinence (FI), sexual dysfunction and oestrogen deficiency if postmenopausal.

Conservative management for women with prolapse

Although there is only one RCT to inform the use of mechanical devices (pessaries or rings), these are often used for women who are unfit for surgery or who wish to avoid surgery. They can be very efficacious, but questions remain about the best type of device, the long-term adverse effects and the use of supplementary treatment such as oestrogen. Further research is required.[8]

Conservative physical treatments such as PFMT are also often recommended as first-line management. A recent update of the relevant Cochrane review[9] has found some evidence supporting the use of PFMT to reduce prolapse symptoms and severity, as well as benefits for urinary and bowel symptoms.

In addition, vaginal oestrogen treatment can be used to reduce symptoms for postmenopausal women, before or after surgery. The evidence supporting its use is limited and inconclusive.[10]

Surgical management for women with anterior or posterior vaginal wall prolapse

The PROSPECT Study compared surgical operations for vaginal wall pelvic organ prolapse:

- anterior vaginal wall prolapse (urethrocele, cystocele, paravaginal defect)
- posterior vaginal wall prolapse (enterocele, rectocele, perineal deficiency).

A woman may present with prolapse of one or both of these sites, and she may be having a primary or a secondary procedure. She may also have a concomitant uterine or vault prolapse or stress UI that requires a continence procedure. For each of these sites there are several alternative traditional surgical techniques, none of which has been properly evaluated in adequately powered multicentre RCTs. Major potential adverse effects include infection, bleeding, mesh exposure and dyspareunia, as well as failure of repair and failure to cure symptoms.

The techniques for performing anterior or posterior repair or implanting mesh or graft can vary widely between gynaecologists. These include the following.

Standard anterior and/or posterior repair

In the standard approach, the vaginal skin is opened in the midline, the fascia is separated from the skin and the fascial defect is plicated (sutured or buttressed). Any redundant vaginal skin is excised and the skin is closed.

Standard repair with mesh inlay

Over the last 10 years, gynaecologists have begun to include small pieces of mesh inlays as an extra support to the fascial defects through which the pelvic organs prolapse, analogous to the use of mesh in hernia surgery.[11] If mesh is used, it can be positioned over or under the fascial defect as a 'mesh inlay' and sutured in place to reinforce the tissues.

The proposed advantage of using mesh is that it will optimise surgical outcome without compromising vaginal capacity or sexual function.[12] The rationale is that it may help to reduce failure rates from breakdown of weakened tissue or failure to identify all fascial defects.[13] Although the mesh materials used may be stronger than the woman's own fascial tissue, the indications for use and choice of materials remain controversial.[13] The extent to which mesh inlays are currently used is unknown, but recent surveys suggest that many gynaecologists are already incorporating mesh into their practice both in the UK and in the USA.[14,15] The decision to use mesh is complicated by the different types available:

- absorbable synthetic (e.g. polyglactin)
- absorbable biological (e.g. fascia lata, porcine dermis)
- combined or semi-absorbable (e.g. polyglactin and polypropylene) *and*
- non-absorbable (e.g. polypropylene).

There are theoretical pros and cons to each, but there is not enough evidence available to allow rigorous comparison.

Mesh insertion using a trocar (introducer device): mesh kits

Some commercial manufacturers of mesh have introduced large mesh systems, analogous to the tension-free vaginal tape (TVT) slings used in incontinence surgery.[16] These commercial devices ('mesh kits') are available for anterior or posterior compartments, or can be used together for both. The mesh is inserted using a trocar (introducer device). This involves blind penetration of pelvic spaces by trocars in order to thread mesh tails into positions from which they support a central mesh layer or hammock, which supports and corrects the prolapse defect. Currently available devices use non-absorbable synthetic mesh, but kits using other types of mesh (combined) have also been used.

These have been actively promoted and introduced to clinical practice without first being evaluated in rigorous independently managed RCTs. These meshes are inserted blindly using introducer devices or trocars that may damage surrounding organs or blood vessels.[17] Prospective studies have suggested that the mesh devices have been used worldwide, but it is not clear whether this is driven by gynaecological preference or commercial marketing pressure. However, clearly some women have been willing to undergo this new technology despite lack of evidence for safety or efficacy.

Evidence for the use of mesh or graft in prolapse surgery

The most recent update of the Cochrane review of surgery[18] for lower compartment prolapse concludes:

> *The use of mesh or graft inlays at the time of anterior vaginal wall repair reduces the risk of recurrent anterior wall prolapse on examination.*

The authors further add:

> *Anterior vaginal polypropylene mesh also reduces awareness of prolapse; however these benefits must be weighed against increased operating time, blood loss, rate of apical or posterior compartment prolapse, de novo stress urinary incontinence, and reoperation rate for mesh exposures associated with the use of polypropylene mesh.*

For posterior wall repairs, the Cochrane review[18] concludes:

> *The evidence is not supportive of any grafts at the time of posterior vaginal repair.*

Repeat surgery for recurrent prolapse

There were no data on the differential effects in women who were having primary as opposed to repeat (secondary) surgery: all of the trials reported both groups of women together despite their potentially different prognoses. There is, therefore, no evidence to suggest whether or not the use of mesh (particularly non-absorbable synthetic mesh, which has the strongest mechanical strength and remains in situ indefinitely) should be reserved for more complex or recurrent prolapse. Although gynaecologists have stated that this is their belief and practice, evidence suggests that the majority (70%) of the current recipients of mesh are having their first prolapse operation.[14]

An Interventional Procedures (IP) review of 503 women and a further recent case series of 289 women drew attention to the high incidence of serious adverse effects (e.g. 2.8% with damage to surrounding organs) in women who were having mesh inserted with blind introducer devices ('mesh kits').[17,19] Our opinion was that until benefits and risks have been properly evaluated, mesh kits using non-absorbable synthetic mesh should be reserved for more complex cases of prolapse. Therefore, in PROSPECT we limited this option to women being treated for a recurrence of prolapse in the site where previous surgery had occurred.

Current recommendations from the National Institute for Health and Care Excellence

An IP review, conducted for the National Institute for Health and Care Excellence (NICE) in 2008, investigated the use of mesh for women who were having anterior and/or posterior vaginal wall prolapse repair.[19,20] The total number of women receiving mesh in this review was 4569: mesh was inserted using an introducer device, trocar or kit in 503 of these women.[19] The IP review also included additional data from non-randomised comparative studies and case series. Using these extra data, non-absorbable synthetic mesh had the lowest failure rate compared with:

- absorbable synthetic mesh [odds ratio (OR) adjusted for bias from study design 0.23, 95% confidence interval (CI) 0.12 to 0.44][19]
- absorbable biological mesh (OR adjusted for bias from study design 0.37, 95% CI 0.23 to 0.59).[19]

On the other hand, the mesh erosion (now termed 'exposure') rates increased from 1% (95% CI 0.1% to 4.0%) with synthetic absorbable mesh to 6% with absorbable biological mesh to 10% with non-absorbable synthetic mesh.[19] The data were too sparse, however, for other reliable statistical analysis. There were insufficient data on women's subjective prolapse symptoms or complications, such as infection, blood loss or dyspareunia, and none on long-term outcomes. Particular safety worries were related to the use of introducer devices (trocars) that were used for the blind insertion of mesh into intrapelvic spaces.[17]

These and other findings were presented to the Interventional Procedures Advisory Committee (IPAC) in January 2008 and their guidance has now been published.[21] The committee recommended that mesh should be used only under special arrangements for clinical governance, consent and audit or research: hence the PROSPECT Study was funded to fill the evidence gap.

Decision to test alternative forms of surgery

There is not enough evidence from RCTs to guide management for women with prolapse. Additionally, the Cochrane and the IP reviews conclude that there is insufficient information about any of the surgical options to guide management of any type of pelvic organ prolapse in any population of women with prolapse.

We identified that the largest group of women are those with anterior and/or posterior prolapse, who constitute around 90% of those having prolapse surgery (including those having a concomitant hysterectomy). The evidence underlying surgery for these women was clearly inadequate, with very little evidence regarding subjective prolapse symptoms, effect on QoL and safety.

Both the Cochrane and the IP reviews[18,19] identified a need for adequately powered RCTs of the use of mesh in prolapse surgery. PROSPECT comprises the largest, adequately powered and independent RCT comparing traditional prolapse operations with new methods incorporating mesh as an inlay or mesh inserted using an introducer system (mesh kit).

Questions addressed by this study

Principal objectives

To determine the effectiveness (including safety) and cost-effectiveness of surgical treatment, primarily in terms of improvement in prolapse symptoms, in women who were having anterior and/or posterior vaginal wall pelvic organ prolapse surgery, separately in two trials:

1. In women who were having a *primary prolapse repair*, the effects of:

    i. a standard repair versus a standard repair using a non-absorbable or combined mesh inlay *and*
    ii. a standard repair versus a standard repair using a biological graft inlay.

2. In women who were having a *repeat prolapse repair*, the effects of:

    i. a standard repair versus a standard repair using a non-absorbable or combined mesh inlay *and*
    ii. a standard repair versus a mesh kit procedure.

The two groups are being considered independently because different surgical options are considered to be appropriate for clinical reasons.

Secondary objectives

1. To determine the differential effects on other outcomes, such as urinary, sexual and bowel function, QoL, general health, need for secondary surgery and adverse effects.
2. To identify possible effect modifiers (e.g. different types of mesh, concomitant procedures, age, complex prolapse types).
3. To establish if the findings of the research, including implications for service delivery, training and introduction of mesh, are generalisable to the UK NHS.

This study assessed which of the most frequently employed techniques for the most common types of prolapse (anterior and posterior vaginal wall prolapse) are most clinically effective and safe. The study also assessed cost-effectiveness. This will guide gynaecologists in their surgical practice and purchasers in their choice of provision of health care. Given the number of prolapse procedures currently performed (28,000 annually in the UK) and the anticipated rise in need for such surgery with an ageing population (a twofold increase in the age group at risk in the next 30 years is predicted), the potential cost implications for the health service are considerable.[6]

Chapter 2 Methods and practical arrangements

Study design

PROSPECT comprised two RCTs within a comprehensive cohort (CC) study. It was designed to determine the effectiveness (including safety) and cost-effectiveness of surgical treatment, primarily in terms of improvement in prolapse symptoms, in women who were having anterior and/or posterior vaginal wall pelvic organ prolapse surgery. Women who were having a primary prolapse repair and those having a secondary prolapse repair were considered independently because different surgical options were deemed to be appropriate for clinical reasons. If a woman did not receive surgery then no follow-up questionnaires were issued.

Important changes to the design after trial commencement

The recruitment rate to both the Primary and Secondary trials proved to be slow initially, partly because of the cost of sourcing all of the mesh types required for the study and lack of availability of certain mesh types, and partly because of some clinicians' preference for one of the mesh types. Therefore, with the agreement of the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC), a decision was made in 2010 to allow surgeons to randomise between no mesh and only one of the mesh options, creating three randomisation strata in both trials. The study design showing the comparisons options available to surgeons is shown in the flow diagram in *Figure 1*.

Clinical centres

Both specialist urogynaecologists and general gynaecologists were eligible to take part if they had extensive experience and training in urogynaecological reconstructive surgery. To participate they had to be prepared to allow treatment allocation to be decided at random for at least a proportion of their patients: the remainder could be entered into the CC study if the patient agreed. Before participating in the trial, the surgeons had to formally choose to which comparisons they were willing to contribute.

Study population

All women under the care of a collaborating surgeon were potentially eligible for inclusion if a decision had been made to have primary or secondary pelvic organ prolapse surgery for anterior and/or posterior vaginal wall prolapse. Women undergoing concurrent hysterectomy/cervical amputation, vault surgery or continence procedures were also eligible. Only women who were unable or unwilling to give competent informed consent, or who were unable to complete study questionnaires, were deemed ineligible.

Two parallel but separate trials were conducted: one among women who were having a primary prolapse repair and the other in women who were having a secondary prolapse repair. For the purposes of PROSPECT, a secondary prolapse was defined as a recurrence of prolapse after a primary procedure, when the recurrence was in the same compartment. If the prolapse was in a different compartment and the original site did not require revision surgery, the woman was classed as having a primary repair of a de novo prolapse.

In addition, women who were unwilling or unsuitable for randomisation were eligible to be followed up using the same protocol as part of the CC study. This included women who were having uterine or vault surgery only.

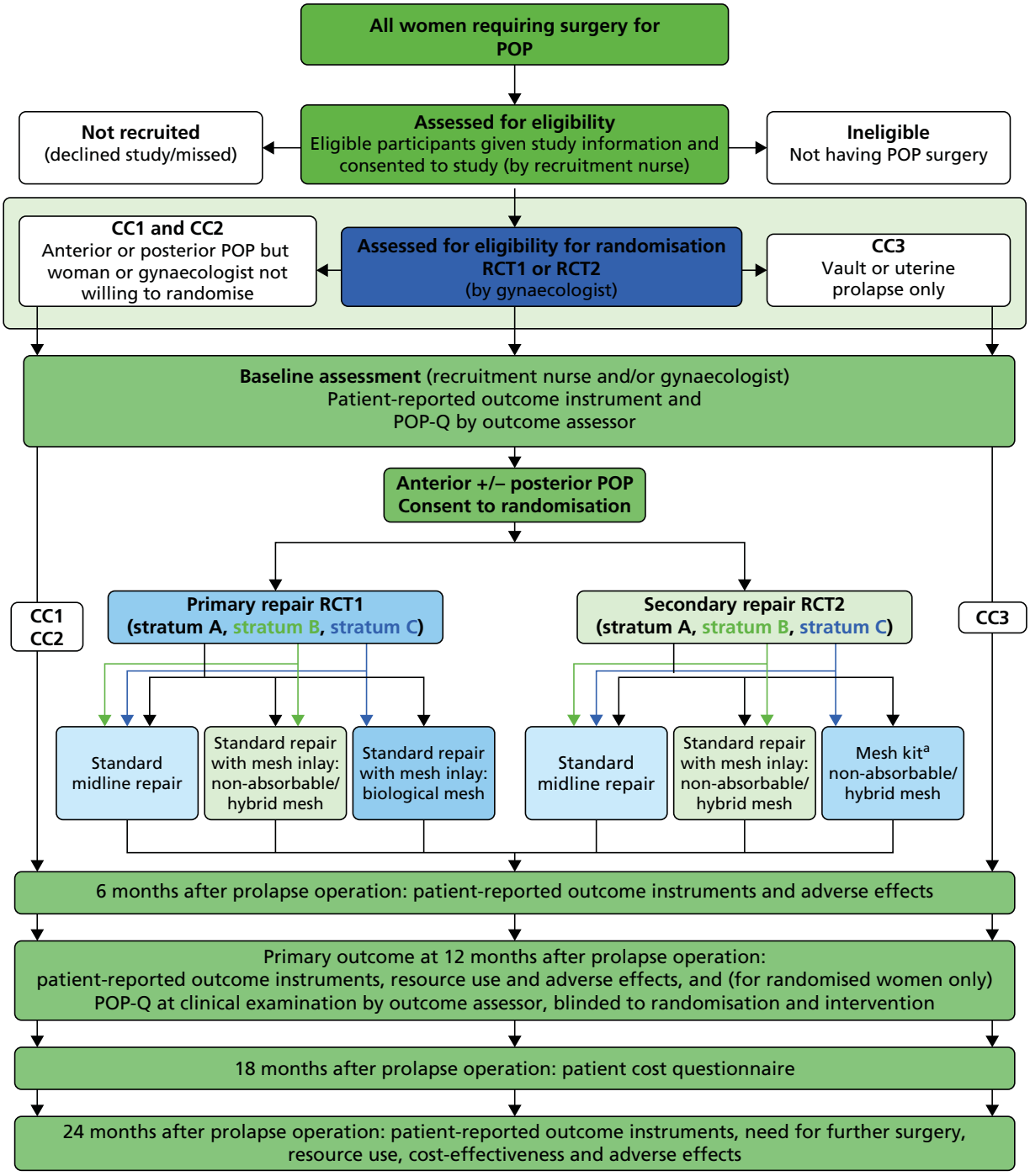


FIGURE 1 Flow diagram of study design. a, Only gynaecologists trained in the use of mesh kits will randomise women to this option. POP, Pelvic Organ Prolapse.

Consent to participate

All women who required pelvic organ prolapse surgery were identified by a dedicated recruitment officer (RO) in each centre. A log was maintained of all of the women meeting the eligibility criterion (admission for prolapse surgery), describing reasons if they did not agree to enter the study or be randomised (see *Appendix 1*). Every woman was allocated a unique study number.

Every eligible woman was given a flyer containing a brief summary of the study when attending the initial clinic appointment (the fliers are reproduced in *Appendix 1*). The women were then given the patient

information leaflet (PIL; see *Appendix 1*) with their admission documents (which could be during the initial clinic appointment or by separate mail, if the woman agreed). Women were given the opportunity to discuss all aspects of the study with their general practitioner (GP) and/or family members before admission, their gynaecologist, the RO, staff at preadmission clinics and/or when admitted to hospital. In addition, all documentation contained the PROSPECT Study office contact details to enable women to obtain information from the study organisers. Signed consent was obtained from each woman to participate (and, if suitable, to be randomised) and followed up after her prolapse surgery by questionnaires and an examination in Gynaecology Outpatients (the latter in randomised women only). The PIL and the consent form (see *Appendix 1*) both refer to the possibility of long-term follow-up, being contacted about other prolapse research and access to their NHS records for these purposes. A letter and GP information sheet were also sent to the woman's GP (see *Appendix 2*). A copy of the consent form, together with a summary of the study, was filed in the woman's hospital notes.

Women who did not wish to be randomised, or who were not suitable for randomisation, were still eligible to be followed up using the same study protocol as part of the CC study. They completed all of the study procedures and documents including follow-up, except for the clinical examination at 12 months.

Women who initially agreed to enter the study but later decided to withdraw or became unable to continue were asked for verbal consent to enable us to retain their existing data and access relevant NHS data. Women who did not agree to participate in the study (randomised or cohort) were logged anonymously along with a minimum data set of age and type of prolapse (anterior, posterior, uterine, vault; primary or secondary procedure) (see *Appendix 1*).

Health technologies being compared

Women were randomised to an intervention according to their surgical history (previous prolapse repair or not), the availability of the mesh (non-absorbable, biological and/or mesh kits) and the skill capacity of their operating gynaecologist (trained in mesh kit use or not). The study design is shown in the flow diagram in *Figure 1*.

If one of the mesh types was temporarily or permanently unavailable (owing to financial constraints) then the women could be randomised to one of the other two arms.

In addition, the expectation was that mesh kits would normally be used only for women who had been randomised to this option. If the operating gynaecologist was not trained in the use of mesh kits then the women under their care could be randomised to one of the other two arms only. Furthermore, in view of the scarcity of data about their safety and efficacy, mesh kits were used only for women who were having a secondary procedure, who have a more complex prolapse problem.

Therefore, women who were having a primary repair were randomised to:

- standard anterior and/or posterior repair (with native tissue only) (reference technique)
- standard anterior and/or posterior repair with a synthetic non-absorbable or hybrid mesh inlay *or*
- standard anterior and/or posterior repair with biological graft inlay.

Women who were having a secondary repair were randomised to:

- standard anterior and/or posterior repair (with native tissue only) (reference technique)
- standard anterior and/or posterior repair with a synthetic non-absorbable or hybrid mesh inlay *or*
- a mesh kit (using an introducer device/trochar) with a non-absorbable or hybrid mesh.

Treatment allocation

After entering contact details, essential baseline information and confirmation of signed consent into the internet-based PROSPECT database, the local researcher was able to randomise the woman (if appropriate) to one of the arms for which she was eligible. Randomisation was carried out as close to the time of surgery as was practical, taking into account the hospital routines and time needed for setting up the operating theatre.

Randomisation utilised the existing proven remote automated computer randomisation application at the study administrative centre in the Centre for Healthcare Randomised Trials [CHaRT, a fully registered UK Clinical Research Network clinical trials unit] in the Health Services Research Unit (HSRU), University of Aberdeen. This randomisation application was available only as an internet-based service.

Randomisation was computer allocated and stratified depending on whether a woman was having a primary or secondary repair. If not eligible for randomisation, the woman was allocated to the CC.

Primary prolapse (de novo) was defined as a prolapse in a compartment that had not been previously repaired. If the woman was having two primary procedures (i.e. both anterior and posterior vaginal wall prolapses required repair) then the randomised allocation applied to both prolapse repairs.

Secondary prolapse was defined as a recurrence of prolapse after a previous procedure, when the recurrence was in the same compartment. If the woman also required a concomitant primary repair of a de novo prolapse in a different compartment, this procedure was chosen on clinical grounds/surgeon choice (i.e. not dictated by the randomisation allocation for the secondary procedure).

If the new prolapse was in a different compartment (de novo) and the original site did not require revision surgery, the woman was classed as having a primary repair of the de novo prolapse and randomised in the Primary trial.

The allocation was computer-generated in ratios of 1 : 1 : 1 for the Primary trial and 1 : 1 : 2 for the Secondary trial. Randomisation was unbalanced in the Secondary trial in favour of mesh kits to account for the skill set of the available surgeons (not all surgeons would be trained in their use). Allocation was further minimised according to:

- the woman's age (< 60 years or ≥ 60 years)
- type of prolapse being randomised (anterior, posterior or both)
- need for a concomitant continence procedure (e.g. TVT) or not
- need for a concomitant upper vaginal prolapse procedure (e.g. hysterectomy, cervical amputation, vault repair) or not *and*
- surgeon.

Clinical management

Within the randomised comparisons, surgeons could use any mesh, graft or mesh kit, providing that any synthetic mesh was monofilament macroporous polypropylene and mesh inlays were secured with peripheral sutures. Surgeons used their mesh material of choice and followed their standard practice so that the technique that they normally used was not modified for the purposes of the trial. All of the other aspects of care were left to the discretion of the responsible surgeon. Each surgeon was asked to complete a surgical standardisation form (see *Appendix 3*) so that their preferred method of surgical repair could be recorded.

We did suggest, however, that the mesh or graft should be inserted under the fascial layer and secured at five points around the periphery of the inlay. If they did so, or wished to secure the inlay in another way

(e.g. attach the inlay to the white line), we asked them to record the method used in the surgical standardisation form, but did not obtain information on whether or not this was actually done for individual participants.

Data collection and processing

Participant-reported outcomes were assessed by self-completed questionnaires at baseline (before surgery; see *Appendix 4*) and self-completed postal questionnaires at 6, 12, 18 (Participant Cost Questionnaire only) and 24 months following surgery (see *Appendix 4*). Where participants ticked more than one box for each question, we recorded this using the worst-case scenario. For randomised women, following one postal reminder, participants who had not returned the questionnaire were telephoned and offered the option of completing the questionnaire over the telephone. For cohort women, only a second postal reminder was issued. A number of other measures were taken to promote ongoing interest in, and commitment to, the trial, including participant newsletters and annual Christmas cards (both randomised and CC women, and collaborators at the clinical centres).

The study-specific questionnaires also included questions about care in general practice, physiotherapy and outpatient consultations related to their prolapse, as well as any complications, readmissions, reoperations and costs. Reported hospital readmissions and complications were confirmed with the clinical centre when required.

Intraoperative and postoperative data were collected by the gynaecologists, supported by ROs. This involved completing a questionnaire (see *Appendix 3*) at the time of surgery, providing details of the operative procedures, complications and resource use, and a short clinical questionnaire (see *Appendix 3*) at the 12-month outpatient review appointment, including a Pelvic Organ Prolapse Quantification (POP-Q) measurement (only randomised women).

Study outcome measures

We identified three primary outcome measures.

1. Women's symptoms of prolapse were measured using the patient-reported Pelvic Organ Prolapse Symptom Score (POP-SS)[22] at 12 months after surgery. This scale was derived from the seven questions that were judged to be most directly related to prolapse symptoms (see *Appendix 4*) and has been shown to reflect the range and intensity of symptoms experienced by women, as well as being responsive to change over time.[23,24] Scores were determined for each of the seven items (ranging from 0 for 'never' to 4 for 'all of the time') with an overall POP-SS out of 28. Participants who only partially completed the seven-item response schedule were assumed to have no symptoms, when no response had been given to any individual items. Women were considered to be symptomatic if their overall score was > 0.
2. QoL (condition-specific) was measured as the woman's rating of the overall effect of prolapse symptoms on everyday life on a 0–10 visual analogue scale (VAS), for which 10 is worst.
3. The primary economic outcome measure of cost-effectiveness was the incremental cost per quality-adjusted life-years (QALYs), based on the EuroQol-5 Dimensions, 3-level version (EQ-5D-3L).[25]

Other outcome measures included objective prolapse measurement; urinary, bowel and sexual symptoms [using the International Consultation on Incontinence (ICI) suite of validated questionnaires];[26] intraoperative and postoperative complications, including the need for additional surgery (repeat surgery for prolapse recurrence or incontinence, and surgery required for adverse effects); cost; and cost-effectiveness.

Objective prolapse measurement

We intended that, at baseline and (for randomised women) at 12 months after surgery, women would have objective measurements of their prolapse compartments. Objective prolapse staging was carried out using the POP-Q system.[27] This measures the maximum descent of each of the three prolapse compartments (anterior, posterior and upper) relative to the hymen (at 0 cm): measurements inside the vagina are negative, whereas those outside are positive. A measure of prolapse (classified from stage 0 to 4) was determined for anterior, posterior and uterine/vault, with the leading edge of the most descended compartment used to define overall stage. An algorithm was used to ensure that POP-Q staging was correctly calculated from the component measurements of the POP-Q [Aa, Ba, C, D, Bp, Ap and total vaginal length (TVL)] in which common recording errors (e.g. Ba measurement less than Aa) were corrected or queried. If data were discrepant, they were corrected by consultation with the local hospital records to obtain additional data. If POP-Q data were missing, we accepted the surgeon's qualitative record of stage, both overall and in individual compartments (i.e. surgeons could specify the stage without giving the POP-Q measurements).

Usually, using the classic Bump *et al.*[27] criteria for the POP-Q system, any measurement from –1 cm (inside the hymen) to 1 cm outside counts as stage 2. However, we further subdivided stage 2 into prolapse at the hymen or within (–1 cm to 0 cm; stage 2a or less) compared with prolapse at > 0 cm (stage 2b).[28,29] Thus, women were classified as having objective prolapse if the leading edge was at any point outside the hymen (measured at > 0 cm, stage 2b, 3 or 4).

Urinary, bowel and sexual symptoms

Symptoms related to other aspects of pelvic floor dysfunction were measured using the ICI suite of validated questionnaires.[26]

Urinary incontinence was assessed using the International Consultation on Incontinence-Urinary Incontinence Short Form (ICIQ-UI-SF). Other urinary symptoms were recorded by the ICIQ-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS). The latter provides subscales for filling, voiding and incontinence symptoms.

The International Consultation on Incontinence Questionnaire (ICIQ)-Bowel Symptom was not finalised when we began PROSPECT. We therefore adapted draft questions to produce a short summary of relevant bowel symptoms. We used similar questions to map on to the ROME criteria to define constipation (*Table 1*).[30]

We assessed vaginal and sexual symptoms using the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS). The ICIQ-VS provides a brief and robust measure to assess the impact of vaginal symptoms and associated sexual matters on QoL and outcome of treatment. It provides subscales for vaginal symptoms, sexual matters and the overall impact of vaginal symptoms on QoL. Women were asked if they were sexually active and, if not, whether or not this was because of their vaginal or prolapse symptoms, or for another reason, including no partner. Women's responses to this

TABLE 1 Comparison between ROME criteria and equivalent questions for the PROSPECT questionnaires

ROME criteria – any two of:	Equivalent PROSPECT questions
Fewer than three bowel movements per week	Stool passing once a week or less
Straining	Straining most or all of the time
Lumpy or hard stools	Hard stools
Sensation of incomplete defecation	Feeling that bowel has not completely emptied most or all of the time
Manual manoeuvring required to defecate	Manual manoeuvre to empty bowel most or all of the time (splinting of perineum or vagina, or digital evacuation of the bowel)
Sensation of anorectal obstruction	*No equivalent PROSPECT question*

question were post-coded to ensure reliability and consistency. Data were included in the analysis of sexual outcomes for women who were sexually active or for women who were sexually inactive because of prolapse symptoms.

Safety reporting

Adverse effects were notified to the study office in a variety of ways. They could be recorded by the centre staff using the recruitment officer case report form (RO CRF; see *Appendix 3*) or at the time of the 12-month clinic review. Women also reported effects and readmissions in the follow-up questionnaires. If an adverse effect was suspected, it was verified if possible.

All related serious adverse effects [serious adverse events (SAEs)] and adverse effects [adverse events (AEs)] were recorded on the serious adverse event report form (see *Appendix 3*). Unrelated SAEs or AEs were not recorded.

Within PROSPECT, a SAE or an AE was defined as 'related' if it occurred as a result of a procedure required by the protocol (i.e. prolapse surgery), whether or not this procedure was the specific intervention under investigation, and whether or not it would have been administered outside the study as normal care. Signs or symptoms of the disease being studied were not considered an adverse effect.

An AE was defined as a SAE if it resulted in death, was life-threatening, required hospitalisation or prolongation of an existing admission, resulted in significant disability/incapacity or was otherwise considered medically significant by the investigator.

Adverse effects that were expected after prolapse surgery are listed below. Any AEs that were deemed to be related and serious but unexpected (i.e. not on the list below) required expedited onward reporting to the sponsor. During the conduct of PROSPECT no unexpected SAEs were reported.

Within PROSPECT the following occurrences were potentially expected:

- Possible (expected) intraoperative occurrences associated with surgery were injury to organs or blood vessels, excess blood loss, blood transfusion, anaesthetic complications, death.
- Possible (expected) occurrences following surgery were thrombosis, infection [urinary tract infection (UTI), sepsis, abscess], pain, urinary retention, bowel obstruction, constipation, mesh erosion, excess blood loss, haematoma, vaginal adhesions, skin tags, granulation tissue, new or persistent urinary tract symptoms, death.

Reported SAEs and AEs were further classified using the International Urogynecological Association (IUGA)/ International Continence Society (ICS) joint terminology and classification of complications that are related directly to the insertion of prostheses (meshes, implants, tapes) and graft in female pelvic floor surgery,[31] and complications related to native tissue female pelvic floor surgery.[32]

Sample size calculation

Primary trial

Pilot data showed a conservative estimate of the standard deviation (SD) of the primary participant-reported outcome POP-SS at 1 year to be eight units, and we considered a difference in means of two units to be a clinically important difference. The sample size calculation for the Primary trial was, therefore, based on a standardised effect size of 0.25. To detect a difference of 0.25 SDs with 90% power and alpha equal to 0.025 (to maintain the nominal *p*-value at 0.05 with tests for two comparisons), we planned to follow-up 400 women in each arm of the primary repair RCT (a total of 1200 participants). The sample size

was inflated to 1450 participants, which allowed for a dropout rate of 17.5%. A trial of this size is also adequately powered to detect important differences in the economic and secondary outcomes.

Secondary trial

It was estimated that 30% of women requiring anterior and/or posterior repair would receive a secondary or subsequent repair. Therefore, during the proposed time period required for recruiting 1450 women to the primary repair RCT above, it was anticipated that approximately 620 women who were having secondary surgery would be randomised to the secondary repair RCT (assuming the same rate of eligibility and willingness to participate as in the primary repair RCT. The total expected recruitment across both trials was therefore 2070 randomised women.

Pilot data indicated that women who were having secondary repairs have a higher level of symptoms at baseline. Therefore, we considered it to be biologically plausible that these women might show a larger benefit from surgical treatment than women who were having their first repair. We therefore calculated that it would be possible to detect, with 90% power and alpha equal to 0.025, a standardised effect size of 0.38, which equates to three points on the Pelvic Organ Prolapse Symptom scale.

Avoidance of bias, including blinding

Group allocation was concealed from the woman and the ward staff, although blinding in theatre was not possible, given that this was a surgical trial. Women were not informed after their surgery of the procedure actually carried out unless they specially requested this information. Outcome assessment was largely by participant self-completed questionnaires, so avoiding interviewer bias.

Where possible, the clinical review at 12 months in outpatients was conducted by research staff who were blinded to allocation, rather than the clinical staff caring for the woman. Although women and research staff were not explicitly informed of which operation was randomly selected, examination may have revealed which operation was actually carried out.

A researcher who was blinded to allocation conducted the data collection, data entry and analysis, using study numbers only to identify women and questionnaires. In the RCTs, an intention-to-treat approach was used in all primary analyses. In addition, all analyses were clearly predefined to avoid bias (see *Appendix 5*).

Statistical analysis

The trial analysis was by intention to treat (all participants remained in their allocated group for analysis), giving the least biased estimate of effectiveness between interventions. Two comparisons were analysed in the primary repair RCT – standard repair compared with synthetic mesh (trial 1, combining the strata 1A and 1B; see *Figure 1*) and standard repair compared with biological mesh (trial 2, combining strata 1A and 1C) and three comparisons were analysed in the secondary repair RCT – standard repair compared with synthetic mesh (trial 3, combining strata 2A and 2B) and standard repair compared with mesh kit (trial 4, combining strata 2A and 2D). Study analyses were conducted according to a statistical analysis plan (SAP), using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) (see *Appendix 5*).

For each time point (baseline, 6, 12 and 24 months), all outcome measures are presented as summaries of descriptive statistics (mean and SD for continuous measures, and proportion for ordinal and dichotomous measures). Comparisons between randomised groups were analysed at 12 months and 24 months using general linear regression models (GLMs). POP-SS, prolapse-related QoL, EQ-5D-3L and readmissions data at 6 months were also analysed. Models were adjusted using minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), the equivalent baseline measure, where appropriate, and (in the primary repair trial) for randomisation stratum.

Continuous outcomes were analysed using linear mixed models, with surgeon fitted as a random effect. POP-Q stage, bowel frequency and satisfaction scales were analysed using ordinal logistic regression, and dichotomous outcomes were analysed using binary logistic regression (proportional odds models with cumulative logits). Estimates of treatment effect size were expressed as the fixed-effect solution for the mean difference (MD) in the mixed models, ORs in the ordinal models and risk ratios (RRs) in the binary models. For all estimates, 95% CIs were calculated and reported.

Subgroup analyses were carried out on the primary outcome in the primary repair RCTs (POP-SS at 1 year) to test subgroup by treatment interaction effects. Subgroups were determined a priori to be age group (< 60 years or ≥ 60 years), type of planned prolapse repair (anterior, posterior or both), planned concomitant continence procedure (yes or no), planned concomitant upper prolapse procedure (yes or no) and parity (0–2 or 3+).

The main analysis was a complete case analysis with no imputation of missing values. Sensitivity analyses, however, were carried out on the primary outcome in the primary repair RCTs (POP-SS at 1 year) to investigate the impact of missing data under various assumptions. The first sensitivity analysis used multiple imputation (MI) using fully conditional specification, which assumed the data to be missing at random. Imputed values were obtained from the generation of 10 data sets and based purely on observed values (minimisation covariates and Pelvic Organ Prolapse Symptom scale scores at baseline). Subsequent sensitivity analyses assumed data to be missing not at random, with scenarios for systematic differences between missing and observed values being examined, and whether or not this might have differed between randomised groups. These analyses adjusted the imputed values in the initial sensitivity analysis by either adding two points to the imputed Pelvic Organ Prolapse Symptom scale scores or subtracting two points. These adjustments were then repeated in one arm only, and repeated again by applying the adjustments in the other arm only. We consider two points on the Pelvic Organ Prolapse Symptom scale to be the minimum clinically important difference and hence a meaningful systematic difference to test in the sensitivity analyses. An additional sensitivity analysis was performed whereby individual unanswered Pelvic Organ Prolapse Symptom scale items were assumed to be missing (rather than assumed to be asymptomatic).

Health-economic evaluation

This section outlines the methods for the trial-based economic evaluation. The methods are applicable to both the analysis of the Primary and Secondary trial data at 1-year and 2-year follow-up. Further detailed methods regarding how the trial data are used to inform the development of a decision-analytic model for the choice of primary prolapse surgical repair, as well as detailed model methods, will be reported in the decision modelling chapter (see *Chapter 9*). Data were analysed at 1-year follow-up, thus following the timeline for the Primary trial outcome analysis. A further analysis was undertaken using 2-year follow-up data, which improve the information relating to recurrence/failure and the associated resource implications in terms of NHS resources consumed as well as QoL. All health-economic analyses within the RCT were based on the intention-to-treat principle. Results from the within-trial economic evaluation are presented as incremental cost-effectiveness ratios (ICERs). The primary framework of analysis for the health-economic evaluation is a cost–utility analysis, reporting results as incremental cost per QALY gained of adopting one treatment approach over another.

For all comparisons of costs and QALYs undertaken in the primary repair trial, results are based on complete case data and are presented for the following comparisons:

1. synthetic mesh repair versus standard repair
2. biological graft repair versus standard repair.

For assessments of the probability of cost-effectiveness, data are considered within a net benefit framework for complete cost and QALY pairs, and for a three-way comparison as per RCT1A (women randomised across all treatment options). For the secondary repair trial, tables of results are presented in a similar manner; however, data from all randomised women are used, not just those randomised to the three-way comparison as above. The justification of the alternative approach is to ensure best use of limited data available. For both the Primary and Secondary trial analyses, we have conducted sensitivity analysis around the choice of data used in the comparisons to explore the impact of these decisions on cost-effectiveness results.

Quality of life (quality-adjusted life-years)

The primary health-economic analysis is based on a cost–utility framework, with results reported as incremental cost per QALY gained. The purpose of a cost–utility analysis is to provide information to health-care decision-makers regarding the scarce allocation of health resources at a health-care level. It allows for a determination of value for money of one treatment approach over another and is used to guide recommendations to UK policy-makers, such as NICE.

The EQ-5D-3L[25] generic QoL instrument was administered to all trial participants at baseline and at 6-month, 1-year and 2-year follow-up. The EQ-5D-3L measure divides health status into five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depressions). Each of these dimensions have three levels, so 243 possible health states exist. EQ-5D-3L responses are presented in graphical format, illustrating the percentage of respondents with any or severe problems on each health domain, split by randomised arms of the trial. The results are presented in accordance with EuroQoL guidelines.[25]

The responses to the EQ-5D-3L questionnaire were valued using UK general population tariffs, based on the time trade-off technique to generate a utility score for every participant within the trial.[25] QoL data derived from the EQ-5D-3L were combined with mortality data from the trial, using the standard assumption that all participants who have died in the trial will have a utility value of 0 from the date of death to the end of follow-up. QALYs were then calculated on the basis of these assumptions, using an area beneath the curve approach, assuming linear extrapolation of utility between time points.

Resource use and costs

The perspective of the primary economic analysis is that of the NHS. A supplementary analysis presents costs from a wider patient/societal perspective. In all cases, resource use and costs relate to consultations in primary and secondary care which are related to women's prolapse or prolapse-related symptoms.

Health services costs

The resource-use data were sourced from participant-completed questionnaires and supplemented with data that were post-coded to patient records for secondary care resource use. Post-coding was conducted by checking all reported cases of secondary care resource use against patient notes to verify reported length of stay, category of care use (so, outpatient or inpatient) and to verify that the reported use of care was for issues related to prolapse and not for some other unrelated reason. Data were obtained from the clinical centres for the price of mesh and clinical expert opinion was sought to bridge any data gaps relating to staff requirements for surgery. National average unit costs were applied to resource-use data to generate total costs to the health services. The sources of unit costs were the *British National Formulary* (BNF) and the NHS Business Services Authority electronic drug tariff online catalogue[33] for medications resource use;[34] Information Services Division (ISD) Scotland[35] and NHS reference costs[36] for secondary care resource-use data; and Personal and Social Services Research Unit (PSSRU) unit costs of health and social care for primary care resource-use data.[37] The costs were reported in 2013–14 UK pound sterling (£). The costs incurred in the second year of follow-up were discounted at a rate of 3.5% per annum. The sensitivity analysis explored the impact of varying the discount rate in accordance with NICE recommendations.[38]

The resource-use data and costs for the health-economic analysis were broken into the following categories of NHS resource use:

- intervention costs (including costs of completing the surgery, preparation costs and hospital resource-use costs in theatre, based on operation time, staff time and other additional treatments)
- postoperative costs (from surgery to discharge) including time on ward, return to theatre and cost of treating any infections or complications
- inpatient costs (cost of any follow-up operations and length of stay in hospital related to prolapse symptoms, including overnight and day-case admissions)
- outpatient costs (including all outpatient contacts over the trial follow-up)
- primary care costs (including GP contacts, occupational therapist, physiotherapist and nurse contacts)
- medications and other treatments related to treating prolapse and UI symptoms.

Unit costs

Costs to the health services are estimated by combining resource-use data with unit costs of resource use. *Table 2* includes a list of all unit costs used in the within-trial economic analysis, together with their source and any assumptions used to develop the unit cost used for analysis. Further details regarding calculations underpinning the unit costs presented in *Table 2* are outlined in more detail in *Appendix 6*. Unit costs applied to the Primary and Secondary trial analyses were similar with the exception of the unit cost of mesh materials to complete the operative procedure.

TABLE 2 Unit costs of resource use for the within-trial economic analysis

Resource-use item	Unit	Cost per unit (£)	Comments	Source
Synthetic mesh material	Per mesh unit	111.09	Average per unit cost of meshes used at all participating sites. Mean cost imputed for centres not returning data	Direct contact with sites/manufacturer price lists
Biological graft materials	Per mesh unit	305.41	Average per unit cost of meshes used at all participating sites using biological graft. Mean cost imputed for centres not returning data	Direct contact with sites/manufacturer price lists
Anterior mesh kits (Secondary trial only)	Per mesh kit	645.45	Average per unit cost of meshes used at all participating sites using anterior mesh kits. Mean cost imputed for centres not returning data	Direct contact with sites/manufacturer price lists
Posterior mesh kits (Secondary trial only)	Per mesh kit	583.00	Average per unit cost of meshes used at all participating sites using posterior mesh kits. Mean cost imputed for centres not returning data	Direct contact with sites/manufacturer price lists
Gynaecologist/ anaesthetist time (consultant)	Per hour	142	If surgery was supervised, assume supervision provided by a consultant grade. Includes qualification costs	PSSRU 2014[37]
Gynaecologist/ anaesthetist time (registrar)	Per hour	124	Includes qualification costs	PSSRU 2014[37]
Gynaecologist/ anaesthetist time (associate)	Per hour	71	Includes qualification costs	PSSRU 2014[37]
Band 5 theatre nurse	Per hour	100	Including qualification costs, cost per 1 hour of patient contact. Assume three band 5 nurses present for all procedures (Dr Karen Cranfield, Aberdeen Royal Infirmary, 2015, personal communication)	PSSRU 2014[37]

continued

TABLE 2 Unit costs of resource use for the within-trial economic analysis (*continued*)

Resource-use item	Unit	Cost per unit (£)	Comments	Source
Band 4 theatre nurse	Per hour	91.59	Per hour of client contact, including qualification costs. Assume one band 4 nurse present for duration of all procedures (Dr Karen Cranfield, personal communication)	
General anaesthesia	Per case	20.60	Based on calculation (see *Appendix 6*)	BNF;[34] personal communication
Spinal anaesthesia	Per case	1.85	Based on calculation (see *Appendix 6*)	BNF;[34] personal communication
Local anaesthesia	Per case	0.40	Based on calculation (see *Appendix 6*)	BNF;[34] personal communication
Surgical antibiotics	Per case	1.06	Assume co-amoxiclav (Augmentin®; GSK, Middlesex, UK); Dr Karen Cranfield, personal communication	BNF;[34] personal communication
Other surgical drugs	Per case	6.45	For general and spinal anaesthesia only; resource use provided by Dr Karen Cranfield (see *Appendix 6* for detailed calculation)	BNF;[34] personal communication
Theatre overheads	Per hour	352.69	Currently excludes consumables	ISD[35] Scotland R140X
Cost of catheterisation	Per catheter	6.25	Assume Folysil® all-silicone catheters, female (Coloplast Ltd, Peterborough, UK); NHS EDT, April 2015 – assume no additional procedure time required if catheterised during surgery	NHS EDT[33]
Vaginal pack	Cost per vaginal pack	4.67	Sorbsan packing (Aspen Medical Europe Ltd, Ashby-de-la Zouch, UK) 30 cm/2 g: £3.47 *plus* Hibitane obstetric cream (Derma UK, Bedfordshire, UK): £1.20	NHS EDT[33]
Other treatments during admission for intervention				
Return to theatre	Per case	814	No data available on time in theatre for returns; conservatively assume duration was 1 hour	Direct cost, ISD[35] R142
Laxatives	Per pack of tablets	3.43	Bisacodyl 5 mg	BNF[34]
Length of stay (gynaecology ward)	Per day	179	Payment by results tariff of £1433 spread over 8 days, so £179 per day	Payment by results, 2014 tariffs[36]
Consultations with secondary and primary health-care professionals/procedures for subsequent treatment or consultations				
New prolapse procedure	Per procedure	2331	Weighted calculation of appropriate HRG codes for surgery for prolapse. See *Appendix 6* for further details	*NHS Reference Costs 2013–14*[36]
New incontinence procedure	Per procedure	1372.48	Weighted average of elective and day-case procedures for HRG code M533 (introduction of TVT/TOT); see *Appendix 6* for calculation details	*NHS Reference Costs 2013–14*[36]
Other readmission	Cost per admission	853.64 (weighted average)	Weighted average of elective in patient/day-case procedures for HRG codes MA22/MA23 minimal/minor genital tract procedures: £803.81 (day case) £1207.85 (> 0 nights' admission) See *Appendix 6* for detailed calculations	Payment by results, 2014 tariffs[36]

TABLE 2 Unit costs of resource use for the within-trial economic analysis (*continued*)

Resource-use item	Unit	Cost per unit (£)	Comments	Source
Outpatient consultation (first attendance)	Per consultation	133	NHS reference costs	*NHS Reference Costs 2013–14*[36]
Outpatient consultation (repeat)	Per consultation	81	NHS reference costs	*NHS Reference Costs 2013–14*[36]
GP visit	Per visit	46	Per 11.7-minute consultation, including qualification costs	PSSRU 2014[37]
Practice nurse	Per visit	13.69	Per 15.5-minute consultation, including qualification costs	PSSRU 2014[37]
Community physiotherapist	Per visit	23.94	Per 30-minute consultation, including qualification costs	PSSRU 2014[37]
Hospital clinical nurse specialist	Per visit	22.50	Based on a per-hour cost of £90 per hour of client contact, assuming average appointment of 15 minutes' duration	PSSRU 2014[37]
Community pharmacist	Per visit	32.50	Based on per-hour cost of £142, including qualification costs, and average appointment duration of 15 minutes	PSSRU 2014[37]
Accident and emergency	Per visit	103	Cost per visit (see *Appendix 6* for more details on calculation)	*NHS Reference Costs 2013–14*[36]
Urodynamics	Per consultation	186	See *Appendix 6* for calculation details. Based on HRG code LB42, assume outpatients	*NHS Reference Costs 2013–14*[36]
Ultrasound scan	Per visit to have scan	52	Diagnostic imaging in outpatients assumed. See *Appendix 6* for further details	*NHS Reference Costs 2013–14*[36]
Other treatments				
Absorbent pads	Per pad – day Per pad – night	0.61 0.66	Based on average across a number of products and data reported in Fader 2008. Data inflated to present-day values. Unit costs multiplied by frequency of leakage to generate cost per woman (see *Appendix 6* for more details)	Fader 2008;[39] PSSRU 2014;[37] HCIS inflation index
Permanent/ indwelling catheter	Per woman (yearly cost)	390.52	Based on a number of assumptions. See *Appendix 6* for calculation details	NHS EDT 2015[33]
Reusable/ intermittent catheter	Per woman (yearly cost)	1816.50	Based on a number of assumptions. See *Appendix 6* for more details	NHS EDT;[33] NHS Warrington[40] Trust documentation for guidance of care
Oestrogen treatment	Per 24-applicator pack	16.72	Estradiol (Vagifem®; Novo Nordisk, West Sussex, UK) vaginal tablets, 10 µg, in disposable applicators. Multiplied by resource-use requirement over follow-up	BNF 2015[34]
Ring pessary	Per pessary	19.98	Average across EDT products (see *Appendix 6* for calculation)	EDT 2015[33]
Shelf pessary	Per pessary	21.51	Average across EDT products (see *Appendix 6* for calculation)	EDT 2015[33]
Drug treatment for bladder problems	Per 56-tablet pack	2.92	Assume tolterodine tartrate, generic version, to cover frequency and urgency symptoms, 2 mg twice daily dose assumed	BNF 2015[34]

EDT, Electronic Drug Tariff; HCIS, Health Care Information Systems; HRG, Healthcare Resource Group; TOT, transobturator tape. Further details of unit cost data are presented in *Appendix 6*.

Intervention costs

The resource-use data required to deliver each intervention were collected prospectively for every participant in the study. The operative details were recorded at the time of surgery (e.g. time in theatre, grade of operating gynaecologist, grade of anaesthetist and grade of surgical supervision if present). The details of concomitant surgery and catheterisation were recorded and incorporated into the costing analysis. The details were sourced from data recorded on the CRFs (see *Appendix 3*). The data from the CRFs were supplemented with centre-specific data for the costs of mesh products. Each centre was asked to provide information on the mesh products used by each surgeon at their site for each trial intervention. The surgeon-specific data on mesh use were costed using NHS list prices, sourced from participating centres financial departments.

For some cases, we were not able to identify mesh costs directly from the participating surgeons. This resulted in some missing data for mesh costs. In such cases, we imputed mean costs of mesh calculated from those surgeons/centres that provided data. It is possible that there is heterogeneity *across* surgeons in terms of the size of mesh product used, or *within* individual surgeons, who may use different mesh sizes on a case-by-case basis. Where possible, we have costed the same (or similar) mesh sizes across different mesh products so as to avoid any bias against individual mesh products. It should be noted that the analysis does not seek to make statements about the effectiveness or cost-effectiveness of individual mesh products, but rather seeks to develop an average cost for each arm of the trial, which is relevant and generalisable to clinical practice in the UK.

When data regarding surgical resource use (particularly regarding the number of supplementary staff present during a typical surgical procedure, such as nurses and theatre assistants) were unavailable from formal records, we have made assumptions based on the clinical opinion of experts working on the trial team. When there was uncertainty in the resource-use estimates to complete the intervention, and when any assumptions were required, sensitivity analysis explored the impact of these assumptions on the total intervention cost and on the estimates of cost-effectiveness.

The purpose of the intervention costing analysis was to find an average procedure cost, based on typically used meshes at participating centres. Data on mesh usage were available from the 35 participating centres. Unit costs of mesh usage were also sourced through a separate costing exercise directly from centres, which were asked to provide NHS list prices. When data were missing for individual mesh products at centres, the average of all mesh products within that category (e.g. synthetic mesh) was assumed and applied as the unit cost. A similar approach was taken for biological graft repair.

Inpatient costs over follow-up

As length of stay is one of the secondary outcomes of the trial, we collected detailed data on inpatient length of stay in relation to both the participant's prolapse surgery and their UI. The hospital-based costs in the immediate aftermath of the surgery (up until date of discharge of the patient) were recorded on the RO CRF (see *Appendix 3*), eliciting information on whether or not the patient returned to theatre for a procedure-related event within 72 hours of having their operation and if catheterisation was required in the first 10 days postoperatively. Longer-term inpatient resource-use data were collected from the participant-completed questionnaires issued at 6-month, 1-year and 2-year follow-up. When participants reported having a hospital readmission, these were checked against patient records to determine the reason for admission. Furthermore, this post-coding exercise identified any participant reporting errors (e.g. patient confused follow-up surgery with index operation; participant double-counted single admissions on both 1-year and 2-year questionnaires; participant misidentified reason for readmission). The costs of additional surgery related to prolapse and/or urinary leakage were estimated using national tariffs, as well as any other inpatient costs. The data collected from both the 1-year and the 2-year follow-ups were used to inform the economic model extrapolating resource use over the patient's lifetime.

Outpatient costs

The participant-completed questionnaires were used to determine outpatient contacts related to the women's prolapse symptoms over follow-up. Again, these were post-coded against patient records to check the accuracy of the data and resolve any discrepancies.

Owing to the post-coding exercises undertaken, we have a high degree of confidence in the estimates of secondary care resource use across the trial for each individual woman returning a questionnaire. Therefore, if a woman did not report a secondary care event, it was assumed that no resource use was incurred. If a woman did not return a questionnaire then data were treated as missing.

Primary care costs

Participants were asked to provide detailed information on contacts with primary care health professionals in relation to their prolapse symptoms and UI (see *Appendix 4*). This included visits to the GP, practice nurse, occupational therapist and physiotherapist at each follow-up time point.

For primary care resource-use questions that are left blank on a returned participant questionnaire, resource use is assumed to be zero. The reason for this is to ensure the best possible use of the available data to generate a reasonably sized complete case data set for the economic analysis. Sensitivity analysis explored the effect of multiply imputed data. As with the secondary care data, if a participant questionnaire is not returned then data are treated as missing.

Total NHS costs

The total costs from the health services perspective were calculated by summing all intervention treatment and follow-up costs related to the respective prolapse repairs for each participant in the data set. If one of the component costs was missing because of a non-returned questionnaire then that participant was dropped from the complete case analysis. If a component cost was missing for primary care consultations then these data were treated according to the assumptions outlined above. The total NHS costs and individual component costs incurred within the second year were discounted by 3.5%.

Participant- and companion-incurred costs and indirect costs, including opportunity costs of time and travel

Participant resource utilisation comprised three main elements: self-purchased health care; travel costs for making return visit(s) to NHS health care (such as petrol, public transport and parking); and time costs of travelling and attending NHS health care (such as time involved away from usual activities or work). All self-purchased health care relate to treatment purchased for the management or treatment of prolapse-related symptoms. Likewise, time and travel costs relate to time spent travelling to and attending hospital or primary care for prolapse symptoms. Estimation of travel costs required information from participants about the number of visits to, for example, their GP or physiotherapist (estimated from the health-care utilisation questions) and the unit cost of making a return journey to each type of health-care provider (from the participant time and travel cost questionnaire; see *Appendix 4*).

The cost of participant time was estimated in a similar manner. The participant was asked, in the participant time and travel cost questionnaire, how long they spent travelling to, and attending, their last visit to each type of health-care provider. Participants were also asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health-care provider. They were further asked if they were accompanied by a friend or a relative. If so, their time and travel costs were also incorporated into the analysis. These data are presented in their natural units, for example hours, and also costed using standard economic conventions, using the Department of Transport estimates for the value of work and leisure time.[41] These unit time costs were then combined with the number of health-care contacts derived from the health-care utilisation questions to elicit a total time and travel cost from a patient perspective.

The data collected through the health services resource-use questionnaire were used to estimate the costs of self-purchased health care, including pads bought by the participant, prescription costs and

over-the-counter medications. The cost to the participant of any self-purchased health care was collected directly within the questionnaire.

Indirect costs were defined as the production losses resulting from treatment when the participant was unable to return to work or was required to take sick leave due to her prolapse problems. The cost of days lost was estimated using the average UK gross hourly wage in the economy. When a participant's own reported costs associated with a specific type of health service visit were missing, the mean cost for that type of visit was imputed. Participants completing the annual health resource utilisation questionnaire were asked how many days they were off work in the last 12 months as a result of prolapse symptoms or problems. Questions were asked at both 1-year and 2-year follow-up. The data were recorded as natural units and multiplied by standard economic costings as reported below (see *Table 3*). The total production losses due to time away from work for non-retirees as a result of prolapse symptoms were estimated and compared across treatment groups.

The unit costs applied to the participant (and companion) time, travel and indirect economic costs data are outlined in *Table 3*. The unit costs were based on standard economic sources and were inflated, where appropriate, to 2014 values. For the purposes of inflation, we utilised the Cochrane economics group inflation calculator application, using International Monetary Fund-reported inflation data.[44]

The data on time and travel costs, participant-incurred medical costs and time away from work or usual activities (to attend medical appointments and as a result of recovery from surgery) were all summed together to generate a total participant cost. The incremental cost differences between groups from a participant perspective were estimated using the same methods outlined in the statistical analysis of economic data detailed in the following section.

Statistical analysis of economic data

The economic analysis was conducted following the intention-to-treat principle. The perspective was predominantly that of the NHS, with a supplementary wider economic and patient perspective conducted. The period of follow-up was 2 years and costs and QALYs in the second year were discounted at a rate of 3.5%. All components of costs were described with the appropriate descriptive statistics where relevant: mean and SD for continuous and count outcomes; numbers and percentages for dichotomous and categorical outcomes (e.g. numbers reporting problems on EQ-5D-3L). All analyses were conducted using Stata® version 14.1 software (StataCorp LP, College Station, TX, USA).

To investigate the potential for skewed cost data (i.e. a small proportion of participants incurring very high costs), we used GLMs, testing alternative model specifications for appropriate fit to the data. The GLM models allow for heteroscedasticity by selecting and specifying an appropriate distributional family for the data. This family offers alternative specifications to reflect the relationship between the mean and variance of the estimates under consideration.[49,50] Two diagnostic actions were performed to select the most appropriate distributional family: (1) a modified Park test, which identified two potentially viable distributional families for costs, namely Gaussian or gamma, and (2) as a check on the most appropriate model, the Akaike information criterion (AIC) was consulted, which identified a Gaussian model with an identity link as having the lowest AIC score and the most appropriate model fit. This suggests a standard ordinary least squares (OLS) model should be fitted for cost data. The next-best model fit according to the AIC criteria was a gamma regression with log link, and this was explored in sensitivity analysis. Regression models applied to cost components (such as 'other treatments' and 'hospital costs') in the analyses above are also assumed to follow the same distributional assumptions as the total cost data. A standard OLS model was also identified as the most appropriate model and applied to the analysis of incremental QALY gains. All analyses were conducted using heteroscedastic robust standard errors (SEs).

Analysis models were run to estimate the incremental effect of treatment group on costs and QALYs. Models were adjusted using minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score.[51]

TABLE 3 Unit costs of participant (and companion) time, travel and wider indirect economic costs of prolapse repairs

Activity	Unit cost (£, 2014)	Assumptions made/notes	Source of data
Unit costs applied to participant and companion travel[a]			
Cost per mile travelled by car	0.45 per mile	HMRC-approved mileage rate (most recent data: year 2013)	HMRC[42]
Car parking charges	Various	Specified in participant questionnaire	Participant-reported data
Cost of public transport fares (bus, train, taxi)	Various	Specified in participant questionnaire	Participant-reported data
Cost of return journey by hospital car	18.00 per return journey	Various costs across NHS Trusts (data from South Devon publicly available and applied to all)	Torbay and South Devon NHS Foundation Trust[43]
Cost of non-emergency patient transport service (via ambulance)	44.65 per return journey	Not included in reference costs since 2011 (therefore indicative cost only) Note: incurred directly by PCTs, so not included in total participant cost calculation	*NHS Reference Costs 2009–10*[36,44,45]
Unit costs applied to participant and companion time			
Paid work	13.21 per hour	Based on average economic wage per week of £518, assuming 39.2-hour working week	ONS; annual survey of hours and earnings 2014[46]
Housework	10.53 per hour	Costs of housework in the NHS (assumed annual salary of £21,000 gross; 2012 values inflated to 2014)	NHS pay review body report 2012[47]
Child care	13.21 per hour	As paid work	ONS 2014[48]
Caring for a friend/ family member	13.21 per hour	As paid work	ONS 2014[48]
Voluntary work	13.21 per hour	As paid work	ONS 2014[48]
Leisure activities	6.54 per hour	Value of non-working time (2010 values inflated to 2014)	TAG data book, autumn 2013[41]
Retired	6.54 per hour	Value of non-working time (2010 values inflated to 2014)	TAG data book, autumn 2013[41]
Unemployed	6.54 per hour	Value of non-working time (2010 values inflated to 2014)	TAG data book, autumn 2013[41]
Ill/disabled (long term, unrelated to prolapse)	6.54 per hour	Value of non-working time (2010 values inflated to 2014)	TAG data book, autumn 2013[41]

HMRC, Her Majesty's Revenue and Customs; ONS, Office for National Statistics; PCT, Primary Care Trust; TAG, Transport Analysis Guidance.

a It is assumed that all of the travel costs were incurred directly by the patients themselves, as it was highly unlikely that the vast majority of women in the study would have qualified for reimbursement of travel expenses from the NHS.

For the Secondary trial, using all available data, analyses were further adjusted for randomised stratum. The coefficient on treatment in the respective linear OLS models is taken as the estimate of incremental costs for use in the economic evaluation.[49,50]

Overall results of the cost–utility analysis are reported as incremental cost per QALY gained for different treatment arms (relative to standard repair). The cost per QALY is presented using the ICER, calculated as the coefficient of treatment effect on costs divided by the coefficient of treatment effect on QALYs from the respective linear regression models. Estimates of the ICER are then compared with the recommended

willingness-to-pay (WTP) decision-making threshold in the UK, currently between £20,000 and £30,000 per QALY gained.[38]

We used non-parametric bootstrapping methods to estimate 95% CIs for treatment effects on costs and QALYs, using 1000 repetitions.[52] These were further used to summarise the uncertainty surrounding the estimated ICERs, which was illustrated using:

i. Incremental scatterplots of bootstrapped repetitions for incremental costs and incremental QALY pairs for the respective mesh treatments compared with standard repair.[53,54] Presentation of the bootstrapped iterations of costs and outcomes on the cost-effectiveness plane allows the reader to see the probability of one intervention outperforming another in terms of cost-effectiveness, illustrating the probability of that said intervention falling into each quadrant of the cost-effectiveness plane being (1) less costly and more effective; (2) more costly and less effective; (3) less costly and less effective; or (4) more costly and more effective.
ii. The bootstrapped estimates of treatment effect were further used to generate cost-effectiveness acceptability curves (CEACs).[54] CEACs were generated using estimates of net monetary benefit (NMB), generated using the bootstrapped replications, in accordance with the net benefit statistic given in *Equation 1*:

$$\text{NMB} = \text{QALY} \times \lambda - \text{cost}, \quad (1)$$

where 'QALYs' and 'cost' are the estimated total QALYs and total costs for a treatment strategy and lambda (λ) represents the ceiling ratio of a decision-maker's WTP for a QALY gained. For the purposes of the base-case analysis, λ is set to £30,000, the upper end of the commonly accepted range of ICERs considered to offer good value for money at NICE. However, for the base-case analyses, a number of alternative threshold values presented at £0, £10,000, £20,000, £30,000 and £50,000 are explored, presented numerically within the tables and visually represented on the CEACs presented.[53,54]

The study initially planned to present results as cost per woman cured for the trial-based analyses. However, it is not clear how 'cure' should be defined. For example, it may be subjective improvement, anatomical improvement or a change in QoL: these are not always in accord with each other. Although many women experienced improvements in their prolapse symptoms, few achieved a state of being completely symptom free. As we are unable to explicitly define cure for the clinical effectiveness analysis, it would be misleading, therefore, to do so for the economic evaluation. The greatest value to decision-makers in the UK NHS relates to an assessment of cost per QALY gained, which is the primary economic outcome and has been used as the basis of all the economic analyses.

Deterministic sensitivity analyses

Although the presentation of CEACs and scatterplots addresses the issue of sampling uncertainty in the data, other assumptions surrounding the most appropriate discount rate and analysis models undertaken may create additional uncertainty, which are not captured in the presented CEACs. Furthermore, the impact of missing data on cost-effectiveness outcomes is explored. All sensitivity analyses (other than the use of imputed data sets) were conducted using complete case 2-year follow-up data for total cost and QALY pairs.

Missing data

We have used a combination of pragmatic and statistical approaches to deal with missing data. Pragmatic approaches have been outlined through this chapter where relevant and were applied to all base-case analyses. As base analyses were conducted using complete case data for cost and QALY pairs, there was a substantial proportion of missing data. This can pose significant problems for data analysis, especially surrounding data reported using participant-completed questionnaires. Therefore, we have undertaken statistical MI of missing data as a sensitivity analysis. The imputation analysis was undertaken using Stata's

multiple imputation (MI) procedure.[55] Missing component costs (e.g. cost of primary care, outpatient care) and utility values were imputed at each questionnaire time point (6 months, 1 year and 2 years).

Components of cost data were imputed, based on linear regression models that were adjusted for minimisation variables, baseline utility and treatment allocation group. Missing utility values were imputed using predictive mean matching, accounting for the five closest estimates. Chained equations were used for the imputations. The imputation procedure predicted 10 plausible alternative imputed data sets, which was found to be sufficient to provide stable estimates. An analysis of incremental costs and outcomes was undertaken across the 10 imputed data sets and combined to generate one imputed estimate of incremental costs and QALYs.

We also explore the impact of changing the discount rate used for second-year costs and QALYs in accordance with NICE best practice recommendations, ranging the discount rate from 0% to 6% per annum. Furthermore, to ensure comparability of our economic analysis with the clinical effectiveness analyses presented in following chapters, we have conducted a secondary analysis for trial-based cost-effectiveness using data from all of the women randomised to the Primary trial arm.

All of the analysis methods for base case, uncertainty and sensitivity analyses were conducted similarly for both the Primary trial analyses (see *Chapter 5*) and Secondary trial analyses (see *Chapter 7*) unless otherwise stated. As noted at the outset, the main difference between the economic analyses across the two chapters pertains to the data considered for the base-case analysis. For the base-case Primary trial analysis, we consider RCT1A (women randomised only across the three-way comparison), whereas for the base-case Secondary trial analysis we consider all women who were having a secondary prolapse surgical repair (RCT2).

Subgroup analyses

We did not identify any additional subgroup analyses that were required to estimate cost-effectiveness for the within-trial analysis.

Decision-analytic model

Owing to the chronic nature of prolapse repair and the potential for different failure rates over time, data from the trial analysis are extrapolated over a longer-term time horizon using a Markov decision-analytic model. The data to populate the model are informed by the trial in terms of costs, utility weights, time to failure and other key parameters. Data on further analysis of trial data to populate the economic model and the modelling methods themselves are reported in *Chapter 9*.

Management of the study

The study office team

The study office was based at CHaRT in Aberdeen and provided day-to-day support for the clinical centres. It was responsible for all data collection (such as mailing questionnaires), follow-up, data processing and analysis. It was also responsible for randomisation and communicating with the centres about PROSPECT-specific issues. PROSPECT newsletters were developed for participants and collaborators to inform everyone of progress and maintain enthusiasm.

The PROSPECT Study office team (Aberdeen-based grant-holders and study office members) met formally at least monthly during the course of the study to ensure smooth running and trouble-shooting.

Project Management Group

The study was supervised by the Project Management Group (PMG), which consisted of the grant-holders and representatives from the study office. The PMG met, in person or by teleconference every 3 months on average.

Trial Steering Committee

The study was overseen by an independent TSC. The membership comprised four independent members (see *Acknowledgements* for membership details), the Chief Investigator and grant-holders. Observers or members of the host university (Aberdeen) and the funders (the NIHR HTA) were invited to attend, as were other members of the PROSPECT Study office. The committee met 11 times between August 2009 and July 2015 at approximately 6-monthly intervals, as decided by the Committee.

Data Monitoring Committee

A separate and independent DMC was convened (see *Acknowledgements* for membership details) and comprised four members: an academic clinician (as the independent chairperson); a gynaecologist, who was not involved in the trial; a statistician with experience of monitoring accumulating RCT data; and a consumer representative.

The members met once to agree terms of reference (August 2009) and a further five times between September 2011 and September 2014 to monitor accumulating data and oversee safety issues. During the period of recruitment to the study, interim analyses were supplied, in strict confidence, to the DMC, together with any other analyses that the committee requested. In the light of these interim analyses, the DMC would have advised the TSC if, in its view:

(a) one of the methods of prolapse surgery had been proven, beyond reasonable doubt, to be different from the control (standard management) for all or some types of women (with respect to either effectiveness or unacceptable safety concerns), *and*
(b) the evidence from the economic data was sufficient to guide a decision from health-care providers about choosing operations.

On each occasion, the DMC recommended continuation of the trial with no change of protocol. All other groups, the TSC, PMG, clinical collaborators and study office team (except the trial statistician, who supplied the confidential analyses) remained ignorant of the interim results considered by the committee.

Chapter 3 Results: all

Between January 2009 and August 2013, 4083 women were identified as potential participants in the PROSPECT Study, of which 3089 (76%) were eligible and gave their consent. The flow of women through the study is shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (*Figure 2*) in line with CONSORT recommendations.[56]

Of the 3089 women participating in the study, 2478 were recruited to the primary group (1352 randomised to the Primary trial (RCT1); 1126 to the Primary CC (CC1), 396 to the secondary group (155 to the Secondary trial (RCT2); 241 to the Secondary CC (CC2) and a further 215 women were in the third CC (CC3) if they were thought to need only uterine or vault prolapse surgery (see *Figure 2*). There were two post-randomisation exclusions that were not included in the study analyses (see *Figure 2*), leaving 3087 women analysed in the PROSPECT Study.

This chapter describes how these women were identified from the women admitted for prolapse surgery in the 37 hospitals, 35 of which recruited women. It reports the baseline differences between the comparable groups of women and their baseline characteristics up to the point of entry to the RCTs or the CCs. The subsequent findings are described in *Chapter 4* (primary prolapse surgery), *Chapter 6* (secondary prolapse surgery) and *Chapter 8* (upper compartment prolapse surgery only: uterine and vault prolapse).

Study recruitment

As described in *Chapter 2*, women who attended gynaecology outpatient departments with symptomatic pelvic organ prolapse and then chose to have prolapse surgery, and women on the waiting list for prolapse surgery, were invited to participate in the PROSPECT Study. Women were asked if they were willing to be randomised to the appropriate options for their type of prolapse, and if not, they were asked to consent to follow-up by questionnaire as part of the CC. The centres and surgeons who participated in PROSPECT, the operations they offered and the numbers they recruited are listed in *Table 4*. The rate of recruitment is illustrated in *Figure 3*.

Non-recruited women

Of the 4083 women approached regarding trial participation, 994 did not enter any of the study groups because they were either missed ($n = 339$), ineligible ($n = 261$) or declined ($n = 394$) (see *Figure 2*). The 994 women who were not recruited to any part of the study are described in *Figure 2*. The most common reasons were 'not interested' (394/994; 40%), a missed opportunity to recruit the potential participant (339/994; 34%), operation cancelled because it was no longer required (117/994; 12%) or because the woman was unfit for surgery (45/994; 5%). Excluding the 339 women who were missed, and the 117 who were found not to need surgery, they represented 538 of 3627 (15%) of all of the potentially eligible women in the centres.

Age was recorded for all recruited women and for 936 of 994 (94%) of non-recruited women. The mean age of non-recruited women was 63.4 years (SD 11.9 years) $n = 936$, compared with 59.7 years (SD 11.0 years) $n = 3089$ for recruited women: the recruited women were significantly younger ($p < 0.001$). We could determine the primary/secondary status of 580 of the ineligible women, and only 13.8% were having further prolapse surgery – the same as the proportion in the recruited women. Therefore, the discrepancy in age was not explained by a larger proportion of women who were having further surgery among the non-recruited women.

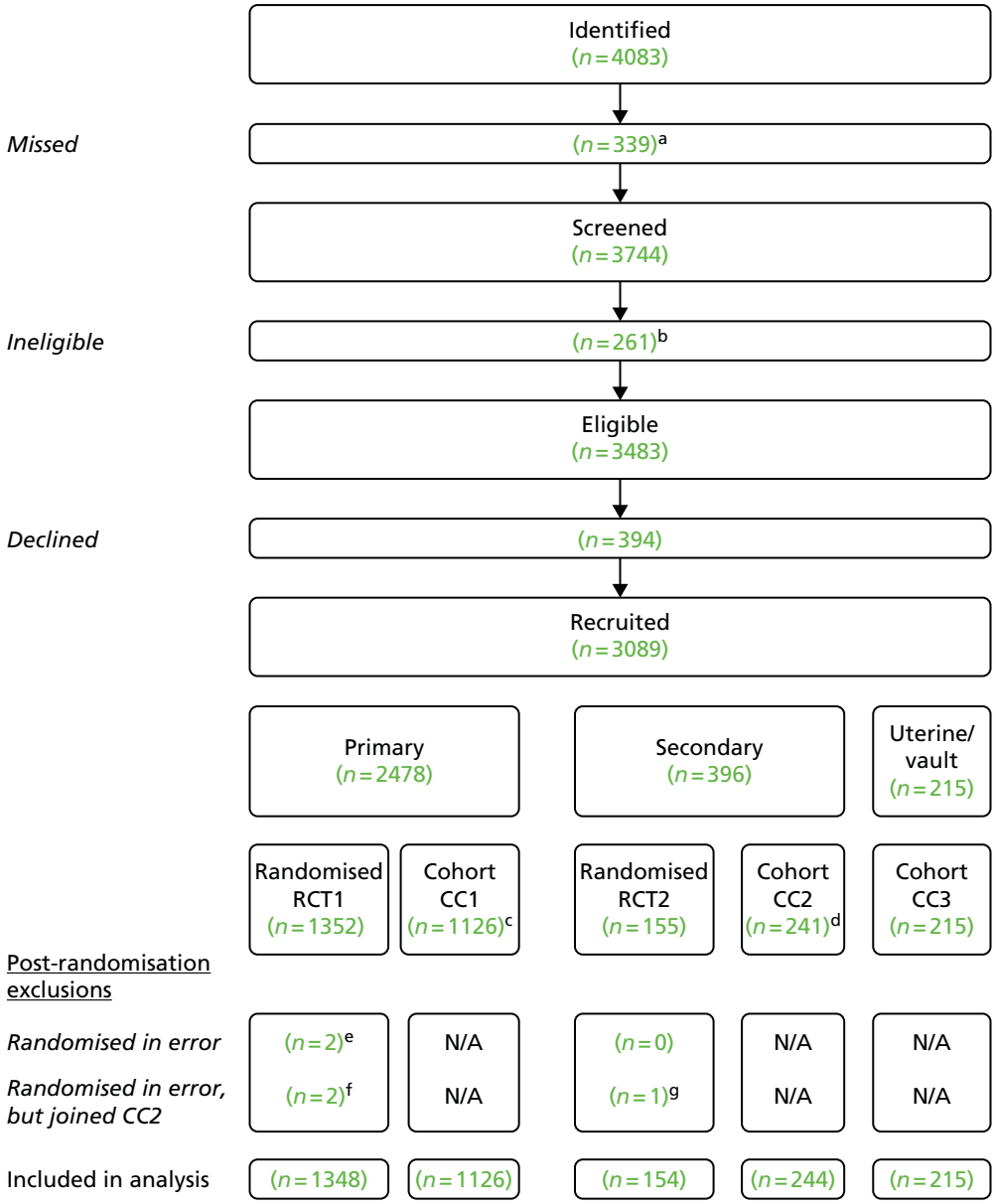


FIGURE 2 CONSORT diagram of women who were recruited to the PROSPECT Study. a, *Missed* [operation performed in a different hospital/Trust, private hospital or by a different consultant; research nurse not aware of the operation date because of cancellations/fast tracking/lack of communication between the research team; surgery date after the end of the study; not consented prior to operation date – research nurse not available; consent form not returned, unable to contact, inappropriate to approach (personal/medical reasons). Eligible for cohort only and trial no longer recruiting to cohort study; Other, e.g. moved away, did not attend, etc.; 339 women]. b, *Reasons for ineligibility (261 women)*: surgery not required [e.g. no prolapse, changed mind about needing surgery (117); removed from waiting list/unfit for surgery (45); unable to give informed consent (32); unable to complete questionnaires (16); other reasons for non-recruitment ('psychological or family problems', 'not clinically or medically suitable to take part in a research study' and 'consultant wished to decide procedure' 32); reason not recorded (19)]. c, *Reasons for non-randomisation in Primary trial (entry to CC1)*: 'Clinical decision' includes 'wanted to use mesh', 'did not want to use mesh' and 'other clinical reason' (379); 'Participant decision' includes 'wanted mesh', 'did not want mesh' 'wanted surgeon to decide' and 'did not want to be randomised' (613); 'Other' reasons include 'mesh unavailable', 'operating surgeon not trained in mesh inlays/kits', 'theatre time issues' and 'not recorded' (134). d, *Reasons for non-randomisation in Secondary trial (entry to CC2*: 'Clinical decision' includes 'wanted to use mesh', 'did not want to use mesh' and 'other clinical reason' (133); 'Participant decision' includes 'wanted mesh', 'did not want mesh' 'wanted surgeon to decide' and 'did not want to be randomised' (96); 'Other' reasons include 'mesh unavailable', 'operating surgeon not trained in mesh inlays/kits', 'theatre time issues' and 'not recorded' (12). e, *Randomised in error*: one woman had baseline comorbidities that made her ineligible for PROSPECT; one woman had prolapse surgery privately after declining to participate but prior to randomisation. f, Two women should have been randomised in the Secondary trial. The women remained eligible for PROSPECT and were followed up in the secondary cohort CC2. g, One woman had secondary prolapse surgery after consenting but prior to randomisation. She remained eligible for PROSPECT and is followed up in the secondary cohort CC2. N/A, not applicable.

TABLE 4 Centres, surgeons and panel of operations offered by individual surgeons, with recruitment numbers

	Primary repair				Secondary repair				Uterine/vault only		
Centre and surgeon	Synthetic mesh	Biological graft	Number randomised	Number recruited to CC1	Synthetic mesh	Mesh kit	Number randomised	Number recruited to CC2	Number recruited to CC3	Uterine	Vault
Aberdeen											
C Bain/Hemming	✓	✓	174	18	✓	✓	19	16	6	4	2
K Cooper	✓	✓	53	17	✓	✓	7	7	1	0	1
M Abdel-Fattah	✓	✗	8	3	✓	✓	0	3	1	0	1
P Terry	✓	✓	5	1	✓	✗	1	0	1	1	0
Ayrshire & Arran											
W Agur	✓	✓	33	106	✓	✓	4	23	2	0	2
D Rae	✓	✗	5	1	✓	✓	0	0	0	0	0
Barnsley											
K Farag	✓	✓	4	10	✓	✗	1	1	0	0	0
M Dass	✗	✗	N/A	14	✓	✓	1	1	0	0	0
Birmingham											
P Toozs-Hobson	✓	✗	35	35	✓	✗	10	22	1	0	1
P Latthe	✓	✗	1	6	✓	✗	1	5	0	0	0
M Parsons	✓	✗	5	7	✓	✗	0	0	0	0	0
Bolton											
A Williams	✓	✓	5	13	✓	✗	0	1	0	0	0
P Chia	✓	✓	3	5	✓	✗	0	1	0	0	0
N Ali-Ross	✗	✗	N/A	1	✗	✗	N/A	0	0	0	0

continued

TABLE 4 Centres, surgeons and panel of operations offered by individual surgeons, with recruitment numbers (*continued*)

	Primary repair				Secondary repair				Uterine/vault only		
Centre and surgeon	Synthetic mesh	Biological graft	Number randomised	Number recruited to CC1	Synthetic mesh	Mesh kit	Number randomised	Number recruited to CC2	Number recruited to CC3	Uterine	Vault
Bradford											
C Ramage	✓	✓	60	25	✓	✓	13	1	0	0	0
S Calvert	✗	✗	0	37	✓	✓	3	1	1	1	0
Brighton											
S Ismail	✓	✓	0	0	✗	✓	1	0	0	0	0
Calderdale											
Y Chan	✓	✓	12	4	✓	✗	3	3	0	0	0
A Bondili	✓	✓	1	0	✓	✗	1	2	0	0	0
Chester											
M Ibraheim	✓	✓	33	45	✓	✓	1	7	2	1	1
L Dinardo	✓	✓	0	3	✓	✗	0	0	0	0	0
Derby											
J Dasgupta	✓	✗	19	4	✓	✗	2	0	2	2	0
V Chilaka	✓	✓	1	0	✓	✗	0	0	0	0	0
Exeter											
M Taylor	✓	✓	14	21	✓	✗	2	8	0	0	0
R Sturley	✓	✓	11	14	✓	✗	4	2	0	0	0
Harrogate											
A Barnett	✓	✗	5	8	✓	✓	1	1	0	0	0
T Jackson	✓	✗	7	6	✓	✓	1	0	0	0	0
Hull											
J Gandhi	✓	✗	16	5	✓	✓	3	4	0	0	0

Centre and surgeon	Primary repair				Secondary repair				Uterine/vault only		
	Synthetic mesh	Biological graft	Number randomised	Number recruited to CC1	Synthetic mesh	Mesh kit	Number randomised	Number recruited to CC2	Number recruited to CC3	Uterine	Vault
Leicester											
D Tincello	✓	✗	31	6	✓	✓	1	2	0	0	0
Luton											
A Fayyad	✓	✗	8	18	✓	✓	0	1	0	0	0
Maidstone											
R Connell	✓	✓	4	3	✓	✓	3	1	0	0	0
Manchester											
A Smith	✓	✓	64	39	✓	✓	11	14	130	25	105
F Reid	✓	✓	59	65	✓	✓	6	8	38	20	18
K Ward	✓	✓	0	0	✓	✗	0	0	0	0	0
Mid Yorkshire											
K Fishwick	✓	✓	37	24	✓	✓	0	5	3	0	3
North Bristol											
P Smith	✗	✓	46	16	✓	✓	1	4	0	0	0
North Cumbria											
M Mater	✓	✗	8	3	✗	✓	0	2	0	0	0
North Devon											
S Eckford	✓	✗	33	54	✓	✓	0	6	2	0	2
O Eskandar	✓	✗	30	73	✓	✓	1	7	3	1	2
Nottingham											
R Parkinson	✓	✗	0	1	✓	✗	0	0	0	0	0
P Hooper	✓	✗	42	29	✓	✗	0	10	3	1	2
M Das	✓	✗	9	2	✓	✗	2	2	0	0	0

continued

TABLE 4 Centres, surgeons and panel of operations offered by individual surgeons, with recruitment numbers (*continued*)

	Primary repair				Secondary repair				Uterine/vault only		
Centre and surgeon	Synthetic mesh	Biological graft	Number randomised	Number recruited to CC1	Synthetic mesh	Mesh kit	Number randomised	Number recruited to CC2	Number recruited to CC3	Uterine	Vault
Portsmouth											
P Hogson	✓	✓	4	6	✓	✗	0	0	0	0	0
Plymouth											
R Freeman	✓	✓	60	65	✓	✗	14	8	4	3	1
L Bombieri	✗	✓	116	30	✗	✗	N/A	5	1	1	0
Preston											
S Prashar	✓	✗	41	41	✓	✓	7	6	0	0	0
Rotherham											
D Patel	✓	✗	6	8	✓	✓	1	2	0	0	0
South Devon											
S Narayanan	✓	✓	58	48	✓	✓	10	5	0	0	0
South Tees											
P Ballard	✓	✓	40	61	✓	✓	5	13	3	2	1
A Khunda	✓	✓	28	15	✓	✓	4	1	1	1	0
St Mary's, London											
V Khullar	✓	✓	3	1	✓	✗	0	0	0	0	0
R Fernando	✓	✓	0	0	✓	✗	0	0	0	0	0
A Digesu	✓	✓	2	0	✓	✗	0	0	0	0	0

Centre and surgeon	Primary repair				Secondary repair				Uterine/vault only		
	Synthetic mesh	Biological graft	Number randomised	Number recruited to CC1	Synthetic mesh	Mesh kit	Number randomised	Number recruited to CC2	Number recruited to CC3	Uterine	Vault
Sunderland											
J Chamberlain	✓	✓	8	0	✓	✗	3	0	1	1	0
Taunton											
A Naguib	✗	✓	25	0	✗	✗	N/A	N/A	1	1	0
West Middlesex											
M Reyad	✓	✓	2	0	✓	✓	0	0	0	0	0
Whipps Cross, London											
S Hussain	✓	✓	6	3	✓	✓	2	1	2	2	0
B Dawlatly	✓	✓	3	0	✓	✓	0	1	1	1	0
S Visvanathan	✓	✓	1	0	✓	✓	0	0	0	0	0
Wolverhampton											
A Elnaqa	✓	✓	17	21	✓	✓	1	6	2	1	1
C Cox	✓	✗	16	22	✓	✓	3	4	1	0	1
K Afifi	✓	✗	1	14	✓	✓	0	3	1	0	1
York											
N Dean	✗	✓	14	11	✗	✗	N/A	4	1	0	1
O Adekanmi	✗	✓	13	24	✗	✗	N/A	10	0	0	0
A Evans	✗	✓	3	14	✗	✗	N/A	4	0	0	0

N/A, not applicable.

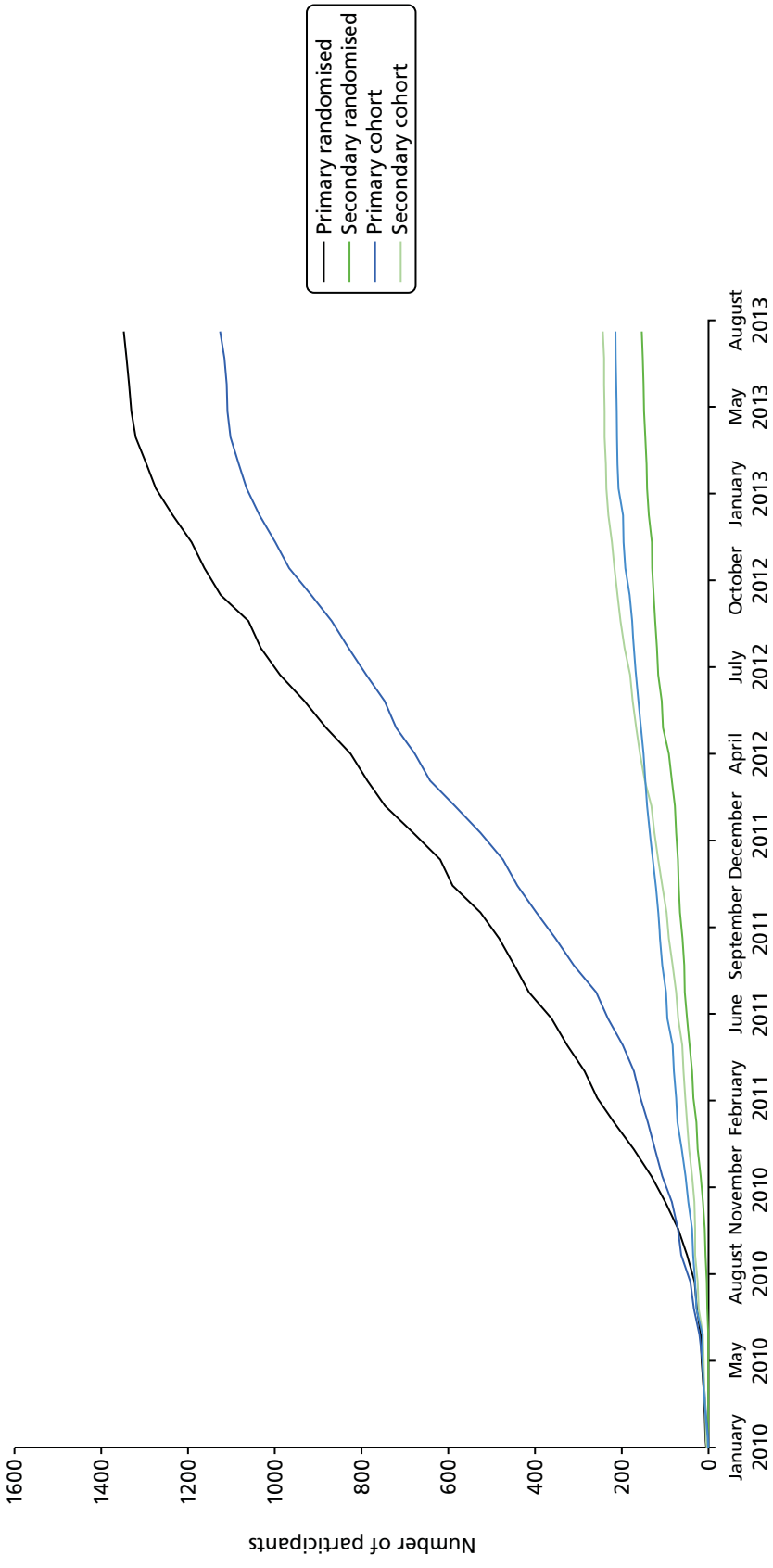


FIGURE 3 Recruitment graph.

The baseline characteristics of the 3087 women who agreed to participate in PROSPECT and were truly eligible for the study are described in *Table 5*. More women were randomised if they were having a primary procedure ($n = 1348$) than those who went into the non-randomised cohort ($n = 1126$), whereas for those having a secondary (repeat) procedure, fewer were randomised ($n = 154$) than not ($n = 244$). At preoperative assessment, a further 215 women were not thought to have an anterior or posterior prolapse that required surgical repair, but did have uterine or vault prolapse. These women are described and compared in detail in *Chapter 8* and are not further analysed in this chapter. However, their data are provided in the tables for completeness (CC3).

Epidemiological characteristics

There were no significant differences between the women who were having primary prolapse surgery who were randomised and those who were not randomised (RCT1 vs. CC1) or between women who were having a second or subsequent repair (RCT2 vs. CC2) according to randomisation status (see *Table 5*). However, those having a repeat repair were, on average, 2.6 years older than those having a primary procedure, and those having uterine or vault surgery only (CC3) were, on average, 1.2 years older than those having primary surgery.

There were also no differences between any of the groups with respect to:

- body mass index (BMI)
- parity (the median number of children was two)
- delivery mode history.

Generic quality of life: EuroQol-5 Dimensions (3-level version)

There were no significant differences between randomised and cohort women who were having first or repeat surgery with respect to EQ-5D-3L scores at baseline. However, those having repeat surgery or uterine or vault operations had slightly lower (worse) scores than those having their first repair.

Previous conservative treatment

Around one-quarter to one-third of women had PFMT for prolapse symptoms, supervised by a physiotherapist, before resorting to surgery, with this being slightly more common for women who were having a repeat procedure (see *Table 5*). Fewer than 15% of women who were having a primary repair, and around 10% of those having a secondary repair, were currently using a vaginal pessary (ring or other type). Just over 15% of women in each group had already had supervised PFMT for UI, and 10–15% had used drug treatment for this problem in the past.

Previous surgery

From *Table 5*, around 10–12% of women in the primary groups were having a second anterior or posterior prolapse repair. However, these women were classed as primary because the compartment that required surgery as part of PROSPECT was the opposite to that which had previously been repaired. This is in accordance with the recommended IUGA/ICS terminology.[57] If the woman thought she had had a previous prolapse repair but it was not possible to discover in which compartment, she was classed as *primary* for the purpose of allocation, but this applied to only 60 women across the five groups.

TABLE 5 Baseline characteristics of all of the PROSPECT participants

Baseline characteristic	Primary RCT: RCT1 (*N* = 1348 women)			Primary cohort: CC1 (*N* = 1126 women)			*p*-value	Secondary RCT: RCT2 (*N* = 154 women)			Secondary cohort: CC2 (*N* = 244 women)			*p*-value	Uterine/vault: CC3 (*N* = 215 women)		
Age, years	59.5	(10.4)	1348	59.4	(11.6)	1126	0.848	62.2	(9.8)	154	62.1	(10.1)	244	0.934	60.7	(12.2)	215
Parity (mean)	2.7	(1.1)	1344	2.5	(1.1)	1115	0.006	2.7	(1.1)	152	2.5	(1.1)	244	0.197	2.7	(1.4)	215
Parity (median)	2.0	(0–9)	1344	2.0	(0–12)	1115		2.0	(1–8)	152	2.0	(0–8)	244		2.0	(0–12)	215
BMI, kg/m^2 (mean)	28.6	(4.8)	1204	28.2	(4.8)	1023	0.034	29.1	(4.9)	134	28.7	(4.8)	220	0.496	27.2	(4.3)	202
BMI, kg/m^2 (median)	27.9	(16–49)	1204	27.5	(17–50)	1023		28.1	(19–46)	134	28.2	(19–44)	220		26.8	(19–40)	202
Delivery mode history																	
Spontaneous vaginal delivery	2.3	(1.3)	1320	2.2	(1.2)	1085	0.219	2.3	(1.3)	147	2.2	(1.3)	237	0.676	2.5	(1.5)	211
Forceps	0.2	(0.5)	1320	0.2	(0.4)	1085	0.120	0.3	(0.5)	147	0.2	(0.5)	237	0.211	0.2	(0.4)	211
Breech	0.0	(0.2)	1320	0.0	(0.2)	1085	0.388	0.1	(0.2)	147	0.0	(0.2)	237	0.191	0.0	(0.2)	211
Elective CS	0.1	(0.3)	1320	0.1	(0.2)	1085	0.381	0.0	(0.1)	147	0.0	(0.1)	237	0.802	0.0	(0.2)	211
Emergency CS	0.0	(0.2)	1320	0.0	(0.2)	1085	0.074	0.0	(0.2)	147	0.0	(0.2)	237	0.741	0.0	(0.1)	211
Vacuum	0.0	(0.2)	1320	0.0	(0.1)	1085	0.206	0.0	(0.1)	147	0.0	(0.1)	237	0.576	0.0	(0.1)	211
EQ-5D																	
Score	0.71	(0.24)	1232	0.71	(0.25)	964	0.839	0.69	(0.25)	145	0.65	(0.26)	213	0.151	0.65	(0.33)	189
Conservative treatment																	
Vaginal pessary	14.4%	193	1342	11.8%	131	1111	0.059	8.7%	13	150	9.9%	24	242	0.681	13.1%	28	213
Physiotherapy for POP	26.7%	358	1340	30.3%	335	1105	0.049	35.5%	54	152	32.1%	76	237	0.480	29.7%	62	209
Physiotherapy for UI	16.1%	215	1338	17.7%	196	1107	0.281	16.4%	25	152	16.4%	39	238	0.987	17.8%	37	208
Drugs for UI	10.3%	137	1335	11.8%	130	1100	0.221	13.8%	21	152	16.4%	39	238	0.493	10.7%	22	205

Baseline characteristic	Primary RCT: RCT1 (*N* = 1348 women)			Primary cohort: CC1 (*N* = 1126 women)			*p*-value	Secondary RCT: RCT2 (*N* = 154 women)			Secondary cohort: CC2 (*N* = 244 women)			*p*-value	Uterine/vault: CC3 (*N* = 215 women)		
Previous surgery																	
Prolapse repair	10.3%	139	1348	12.2%	137	1126	0.144	100.0%	154	154	100.0%	244	244	N/A	43.7%	94	215
Anterior	5.0%	67	1348	5.0%	56	1126	0.997	81.2%	125	154	86.1%	210	244	0.192	26.5%	57	215
Posterior	3.0%	40	1348	3.6%	40	1126	0.413	55.2%	85	154	57.0%	139	244	0.728	19.1%	41	215
Anterior and posterior	0.0%	0	1348	0.0%	0	1126	N/A	36.4%	56	154	43.0%	105	244	0.187	13.0%	28	215
Vault	1.5%	20	1348	2.6%	29	1126	0.052	9.7%	15	154	14.8%	36	244	0.145	11.6%	25	215
Unknown	1.6%	22	1348	2.3%	26	1126	0.224	1.3%	2	154	1.2%	3	244	0.952	3.3%	7	215
Hysterectomy	26.8%	361	1348	29.8%	336	1126	0.092	62.1%	95	153	73.0%	178	244	0.023	67.9%	146	215
Vaginal	9.8%	132	1348	10.7%	121	1126	0.436	36.6%	56	153	44.7%	109	244	0.112	32.1%	69	215
Cervical amputation	1.9%	25	1348	2.7%	30	1126	0.174	8.5%	13	153	7.0%	17	244	0.575	2.3%	5	215
Abdominal	16.9%	228	1348	18.7%	210	1126	0.260	25.5%	39	153	27.0%	66	244	0.732	34.9%	75	215
UI surgery	6.0%	80	1341	7.7%	86	1111	0.082	13.2%	20	151	16.4%	39	238	0.400	13.7%	29	211

BMI, body mass index; N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Very few women who were having a primary repair had had a previous vault repair (around 2%), whereas this was more common for women who were having a repeat repair (10–15%).

Fewer than 10% of women who were having their first repair had previous concomitant continence surgery, whereas it was around 15% for those having a repeat repair, a similar proportion to those having an upper compartment procedure only.

Slightly more women had undergone previous uterine surgery (hysterectomy) in the cohorts than in the randomised groups, both for primary and secondary repairs, but this was statistically significant for only the latter ($p = 0.023$; see *Table 5*). Among women who were having their first repair, more had undergone a previous abdominal hysterectomy than a vaginal hysterectomy (or cervical amputation, which is necessarily carried out via the vagina), whereas for those having a second repair, more women had had a previous vaginal hysterectomy than abdominal. Overall, many more women who were having a repeat repair had already had a previous hysterectomy than those having their first repair (around 62–73% of the Secondary group and just under 30% of the Primary group).

Planned surgery

Although it is known that in about 20% of case the actual operation carried out differs from that planned in advance,[29] PROSPECT was designed so that women would remain in the group to which they were allocated, irrespective of the actual procedure performed. In order to randomise women appropriately, taking account of minimisation criteria, gynaecologists had to specify in advance which compartments they thought would need to be repaired.

Gynaecologists planned surgery for the women based on their preoperative findings on examination. *Table 6* shows that just under half of the women were expected to require an anterior repair, about one-quarter a posterior repair, and the remainder both procedures. The proportions were the same whether the procedure was primary or repeat, and whether or not the women were randomised.

In terms of concomitant prolapse surgery, hysterectomy was planned more frequently in women in the Primary trial, whereas in the Secondary trial more women were thought to need a vault repair (see *Table 6*). The need for vault repair was higher in both cohort groups (although statistically significant only in the larger Primary trial), suggesting that women who might need a concomitant upper compartment procedure were less likely to be randomised. Cervical amputation was planned much less commonly (< 2% in any group). Between RCT and CC cohort groups, there was little difference in the frequency of women who were thought to need continence surgery, but the proportions were fewer in the secondary groups.

Preoperative objective measurements

Although gynaecologists were expected to use the POP-Q,[27] not all did so. However, attempts were made to locate important missing data from the centres, using alternative sources such as medical notes, correspondence and asking the centre staff. The aim was to have as complete a set of prolapse staging as possible, separately in each compartment. The leading edge of the most descended compartment relative to the hymen was used for overall (POP-Q) stage.

The most common stage for women who were having an anterior or posterior repair was stage 2 (around 60%; *Table 7*). The majority of the remaining women were stage 3, and very few were stage 4, or indeed stage 0 or 1. Using a more strict definition of 'leading edge of prolapse beyond the hymen (> 0 cm on POP-Q; stage 2b, 3 or 4), 61–67% of women in the Primary trial and 52–58% in the Secondary trial had an objective prolapse (see *Table 7*). Significantly more women had objective prolapse in the randomised arm of the Primary trial than in the primary cohort; the small excess among cohort women in the Secondary trial was not significant.

TABLE 6 Planned surgery (all PROSPECT participants)

Type of surgery	Primary RCT: RCT1 (*N* = 1348 women)			Primary cohort: CC1 (*N* = 1126 women)			*p*-value	Secondary RCT: RCT2 (*N* = 154 women)			Secondary cohort: CC2 (*N* = 244 women)			*p*-value	Uterine/vault: CC3 (*N* = 215 women)		
Anterior repair	44.8%	604	1348	44.5%	501	1126	0.876	46.8%	72	154	45.9%	112	244	0.868	0.0%	0	215
Posterior repair	25.8%	348	1348	26.8%	302	1126	0.572	26.0%	40	154	26.6%	65	244	0.883	0.0%	0	215
Anterior and posterior repair	29.4%	396	1348	28.7%	323	1126	0.706	27.3%	42	154	27.5%	67	244	0.968	0.0%	0	215
Upper compartment repair only	0.0%	0	1348	0.0%	0	1126	N/A	0.0%	0	154	0.0%	0	244	N/A	100.0%	215	215
Concomitant prolapse surgery																	
Vaginal hysterectomy	34.7%	468	1348	32.7%	368	1126	0.286	13.6%	21	154	6.6%	16	244	0.018	10.2%	22	215
Abdominal hysterectomy	0.1%	1	1348	0.4%	4	1126	0.121	0.6%	1	154	0.8%	2	244	0.848	2.3%	5	215
Cervical amputation	1.7%	23	1348	1.4%	16	1126	0.571	0.0%	0	154	0.8%	2	244	0.260	1.9%	4	215
Vault repair	15.5%	209	1348	20.9%	235	1126	0.001	22.7%	35	154	27.0%	66	244	0.335	90.7%	195	215
Concomitant UI surgery	11.0%	148	1348	13.3%	150	1126	0.075	4.5%	7	154	6.6%	16	244	0.402	4.2%	9	215

N/A, not applicable.
Dichotomous variables are presented as '% *n N*'.

TABLE 7 Preoperative objective measures of prolapse (all PROSPECT participants)

POP-Q measurement/stage	Primary RCT: RCT1 (*N* = 1348 women)			Primary cohort: CC1 (*N* = 1126 women)			*p*-value	Secondary RCT: RCT2 (*N* = 154 women)			Secondary cohort: CC2 (*N* = 244 women)			*p*-value	Uterine/vault: CC3 (*N* =215 women)		
POP-Q measurement (cm)																	
Ba (posterior edge)	0.5	(2.1)	1190	0.4	(2.1)	860	0.792	0.1	(2.0)	143	0.3	(2.1)	201	0.360	2.0	(2.4)	193
C (cervix/vault)	–3.4	(3.4)	1109	–3.2	(3.3)	812	0.414	–4.1	(3.2)	135	–3.3	(3.5)	191	0.037	0.2	(3.8)	184
Bp (posterior edge)	–0.4	(1.9)	1187	–0.5	(1.8)	855	0.121	–0.5	(2.0)	140	–0.3	(2.1)	194	0.484	0.7	(2.7)	192
TVL	8.4	(1.7)	1090	8.5	(1.8)	809	0.029	8.2	(2.3)	129	8.0	(1.5)	179	0.422	8.5	(1.7)	159
Overall POP-Q stage																	
0	0.2%	2	1293	0.0%	0	997	< 0.001	0.0%	0	153	0.4%	1	227	0.200	0.0%	0	203
1	1.0%	13	1293	2.0%	20	997		0.0%	0	153	0.9%	2	227		1.5%	3	203
2	56.3%	728	1293	61.9%	617	997		68.0%	104	153	60.8%	138	227		37.4%	76	203
3	39.9%	516	1293	34.1%	340	997		30.7%	47	153	31.3%	71	227		47.3%	96	203
4	2.6%	34	1293	2.0%	20	997		1.3%	2	153	6.6%	15	227		13.8%	28	203
2b, 3 or 4	*66.9%*	*825*	*1233*	*60.7%*	*537*	*884*	*0.004*	*52.1%*	*76*	*146*	*57.8%*	*119*	*206*	*0.288*	*82.1%*	*160*	*195*

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

Clinical baseline data

Prolapse symptoms at baseline

The overall prolapse symptom score (POP-SS) was around 13.5 in the women who were having their first repair [with no difference between the randomised and cohort women (13.7 vs. 13.3; *Table 8*)] but significantly higher in those having a repeat procedure [with no difference between the randomised and cohort women (14.4 vs. 14.9)]. Using a POP-SS of 0 to indicate absence of symptoms, > 99% of women had at least one symptom. The women who were having a uterine or vault repair only (CC3) had an intermediate score, with a mean POP-SS of 14.5 (see *Table 8*). The latter group will be further described separately in *Chapter 8*.

The most common individual prolapse symptom was 'a feeling of something coming down from or in your vagina', which was reported in > 90% of women, with two-thirds of women reporting this most or all of the time (*Table 9*). The QoL score ('overall, how much do your prolapse symptoms interfere with your everyday life?') ranged from 6.6 to 7.0 of 10 (see *Table 8*). About half of the women found the prolapse to pose hygiene problems, and about one in five needed to relieve pressure or discomfort from the prolapse using their fingers (see *Table 9*). Women had been symptomatic for ≥ 3 years and bothered by their symptoms for about a year less.

Among women having a recent repair, there was a significant difference in duration of symptoms in the cohort women (CC2, 3.8 years) compared with the randomised women (RCT2, 3.8 vs. 2.8 years; $p = 0.034$).

There were no other differences between any of the groups with respect to:

- duration of prolapse symptoms (the mean duration ranged from 2.8 to 4.3 years)
- duration of bothersome symptoms (the mean ranged from 2.4 to 3.2 years of bother)
- mean prolapse symptom score (the mean ranged from 13.3 to 14.9 out of a maximum score of 28 on the Pelvic Organ Prolapse Symptom scale.

Urinary symptoms at baseline

Using the ICIQ-UI-SF,[26] up to 80% of women reported at least some UI; however, 20–23% had more severe leakage based on a higher score (*Table 10*). The most common type of UI was stress UI: women were counted as symptomatic if they had the symptom 'most or all of the time'. There were no systematic differences between the groups of women.

Bowel symptoms at baseline

Using ROME[58] criteria to define bowel symptoms, around one-quarter or more of the women reported constipation (*Table 11*). Over one-third had FI, defined as loss of solid or liquid stool, but not including loss of flatus (wind). Three-quarters of the FI was 'passive,' defined as 'not accompanied by bowel urgency'. There were no systematic differences between the groups of women at baseline.

Vaginal and sexual symptoms at baseline

We used the ICI-validated instruments to measure a variety of vaginal and sexual symptoms. These were common, and had important effects on QoL. Although the majority of women were not sexually active, in about 40% of women this was most often attributable to their prolapse symptoms (*Table 12*). Among the women who were sexually active, or whose reason for no sex life was 'due to prolapse symptoms', around 10% had dyspareunia at baseline. There were no systematic differences between the groups of women.

Comparison between women who were having a first repair and those who were having a repeat repair

From *Table 5*, it might seem that around 11% of women in the primary repair groups (RCT1, CC1) had had previous prolapse surgery, but the compartment that required surgery was the opposite to that which

TABLE 8 Prolapse symptoms at baseline (all PROSPECT participants)

Symptom	Primary RCT: RCT1 (*N* = 1266 women)			Primary cohort: CC1 (*N* = 997 women)			*p*-value	Secondary RCT: RCT2 (*N* = 148 women)			Secondary cohort: CC2 (*N* = 221 women)			*p*-value	Uterine/vault: CC3 (*N* = 202 women)		
POP-SS at baseline																	
Score	13.7	(5.9)	1266	13.3	(5.8)	995	0.068	14.4	(5.4)	148	14.9	(5.8)	220	0.427	14.5	(6.6)	197
Other measures of prolapse symptoms at baseline																	
Symptoms (years)	3.6	(5.0)	1218	3.6	(5.0)	948	0.868	2.8	(3.3)	142	3.8	(5.3)	205	0.034	4.3	(5.2)	184
Bother (years)	2.6	(4.1)	1170	2.5	(3.4)	916	0.392	2.4	(3.0)	140	2.9	(4.1)	201	0.203	3.2	(3.7)	177
Number of women symptomatic	99.6%	1261	1266	99.6%	991	995	0.979	100.0%	148	148	99.5%	219	220	0.411	100.0%	197	197
Prolapse-related QoL score	6.6	(2.7)	1251	6.7	(2.7)	969	0.220	6.9	(2.3)	148	6.9	(2.5)	216	0.977	7.0	(2.9)	193

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

TABLE 9 Individual prolapse symptoms at baseline (all PROSPECT participants)

Symptom	Primary RCT: RCT1 (*N* = 1266 women)			Primary cohort: CC1 (*N* = 997 women)			*p*-value	Secondary RCT: RCT2 (*N* = 148 women)			Secondary cohort: CC2 (*N* = 221 women)			*p*-value	Uterine/vault: CC3 (*N* = 202 women)		
Individual prolapse symptoms																	
SCD any	92.8%	1175	1266	93.9%	934	995	0.319	93.9%	139	148	94.5%	208	220	0.799	97.0%	191	197
SCD freq.	66.1%	837	1266	66.5%	662	995	0.834	73.0%	108	148	71.4%	157	220	0.736	77.7%	153	197
Pain any	80.7%	1022	1266	81.6%	812	995	0.595	80.4%	119	148	85.9%	189	220	0.161	85.8%	169	197
Pain freq.	34.4%	436	1266	36.4%	362	995	0.337	37.2%	55	148	45.0%	99	220	0.135	47.7%	94	197
Abdo. any	81.1%	1027	1266	79.2%	788	995	0.253	83.8%	124	148	85.9%	189	220	0.575	80.2%	158	197
Abdo. freq.	34.2%	433	1266	33.4%	332	995	0.677	37.8%	56	148	45.0%	99	220	0.172	35.0%	69	197
Back any	72.9%	923	1266	68.6%	683	995	0.027	73.6%	109	148	82.7%	182	220	0.036	70.6%	139	197
Back freq.	29.9%	379	1266	25.8%	257	995	0.031	35.1%	52	148	34.1%	75	220	0.836	28.9%	57	197

Symptom	Primary RCT: RCT1 (*N* = 1266 women)			Primary cohort: CC1 (*N* = 997 women)			*p*-value	Secondary RCT: RCT2 (*N* = 148 women)			Secondary cohort: CC2 (*N* = 221 women)			*p*-value	Uterine/vault: CC3 (*N* = 202 women)		
Strain blad. any	71.3%	903	1266	69.5%	692	995	0.357	70.9%	105	148	67.7%	149	220	0.513	69.0%	136	197
Strain blad. freq.	29.0%	367	1266	26.1%	260	995	0.132	27.0%	40	148	29.5%	65	220	0.600	32.5%	64	197
Blad. not empty any	82.5%	1044	1266	83.0%	826	995	0.731	85.1%	126	148	82.7%	182	220	0.540	84.3%	166	197
Blad. not empty freq.	38.3%	485	1266	35.7%	355	995	0.199	41.9%	62	148	35.9%	79	220	0.247	39.6%	78	197
Bowel not empty any	82.5%	1044	1266	79.0%	786	995	0.037	85.1%	126	148	85.0%	187	220	0.972	80.2%	158	197
Bowel not empty freq.	37.2%	471	1266	30.8%	306	995	0.001	34.5%	51	148	43.2%	95	220	0.094	31.0%	61	197
Actions necessitated by prolapse symptoms																	
Fingers to ease discomfort	20.8%	259	1247	19.4%	189	972	0.440	16.4%	24	146	16.0%	34	213	0.904	28.0%	53	189
Extra hygiene measures	51.7%	640	1239	47.9%	465	970	0.083	51.7%	74	143	56.1%	120	214	0.421	58.9%	113	192
Fingers to help empty bladder	3.7%	46	1249	4.9%	48	976	0.151	4.8%	7	147	3.7%	8	214	0.632	11.1%	21	190
Fingers to help empty bowel	10.8%	134	1244	11.2%	109	972	0.741	5.5%	8	145	8.3%	18	217	0.316	4.7%	9	192
Digital evacuation of bowel	7.5%	93	1246	8.4%	82	977	0.419	6.3%	9	144	5.1%	11	215	0.646	4.6%	9	196

SCD, something coming down.

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse symptoms

Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time.; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely? (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad. any*: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.

Actions necessitated by prolapse symptoms

Fingers to ease discomfort: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time). *Digital evacuation of bowel*: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time).

TABLE 10 Urinary symptoms at baseline (all PROSPECT participants)

Symptom	Primary RCT: RCT1 (*N* = 1266 questionnaires)			Primary cohort: CC1 (*N* = 997 questionnaires)			*p*-value	Secondary RCT: RCT2 (*N* = 148 questionnaires)			Secondary cohort: CC2 (*N* = 221 questionnaires)			*p*-value	Uterine/vault: CC3 (*N* = 202 questionnaires)		
Any incontinence	77.5%	979	1263	76.1%	756	994	0.415	81.0%	119	147	74.7%	165	221	0.159	75.0%	147	196
Incontinence-related QoL score	7.2	(5.7)	1251	7.2	(5.8)	974	0.761	7.6	(5.6)	146	7.0	(5.8)	220	0.761	7.1	(6.0)	192
Severe incontinence	20.5%	257	1251	22.0%	214	974	0.413	20.5%	30	146	20.0%	44	220	0.898	22.9%	44	192
ICIQ-UI-SF score	3.6	(3.4)	1224	3.7	(3.5)	956	0.440	3.8	(3.4)	145	3.5	(3.3)	211	0.399	3.8	(3.6)	181
Stress UI	24.4%	275	1125	25.0%	220	881	0.786	19.6%	27	138	18.8%	36	192	0.853	22.2%	38	171
Urgency UI	9.6%	121	1255	10.6%	104	982	0.459	10.2%	15	147	10.7%	23	215	0.880	11.9%	23	194
Overactive bladder	5.8%	72	1243	5.6%	55	977	0.870	6.8%	10	147	9.0%	19	211	0.453	7.3%	14	192
ICIQ-FLUTS filling score	5.3	(2.9)	1235	5.3	(2.9)	970	0.942	6.0	(2.9)	146	6.0	(3.1)	208	0.950	5.7	(3.1)	189
ICIQ-FLUTS voiding score	3.1	(2.6)	1244	3.1	(2.6)	975	0.850	3.4	(2.7)	146	3.2	(2.8)	212	0.510	3.4	(2.7)	192
ICIQ-FLUTS incontinence score	6.1	(4.2)	1111	6.1	(4.3)	858	0.754	6.0	(4.1)	136	6.2	(4.3)	190	0.761	5.7	(4.2)	169

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*: nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

TABLE 11 Bowel symptoms at baseline (all PROSPECT participants)

Symptom	Primary RCT: RCT1 (*N* = 1266 questionnaires)			Primary cohort: CC1 (*N* = 997 questionnaires)			*p*-value	Secondary RCT: RCT2 (*N* = 148 questionnaires)			Secondary cohort: CC2 (*N* = 221 questionnaires)			*p*-value	Uterine/vault: CC3 (*N* = 202 questionnaires)		
Bowel frequency																	
> 3 times a day	5.8%	72	1250	5.0%	49	977	0.262	5.6%	8	144	7.3%	16	218	0.817	4.6%	9	195
1–3 times a day	33.9%	424	1250	36.2%	354	977		37.5%	54	144	41.3%	90	218		32.3%	63	195
About once a day	40.2%	502	1250	40.4%	395	977		36.1%	52	144	33.0%	72	218		39.0%	76	195
Once every 2–3 days	17.1%	214	1250	16.6%	162	977		16.7%	24	144	15.6%	34	218		20.0%	39	195
Weekly or less	3.0%	38	1250	1.7%	17	977		4.2%	6	144	2.8%	6	218		4.1%	8	195
Constipation	29.0%	358	1236	24.6%	239	970	0.023	25.5%	37	145	31.0%	66	213	0.262	24.0%	46	192
Bowel urgency	12.0%	150	1253	10.8%	106	985	0.372	9.6%	14	146	8.6%	19	220	0.755	10.7%	21	197
FI (any)	34.4%	431	1252	33.4%	328	982	0.612	39.5%	58	147	36.4%	80	220	0.549	32.3%	63	195
Passive FI	73.3%	315	430	75.8%	248	327	0.420	82.8%	48	58	81.3%	65	80	0.820	71.4%	45	63
Active FI	26.7%	115	430	24.2%	79	327		17.2%	10	58	18.8%	15	80		28.6%	18	63
Severe FI	12.7%	159	1252	11.2%	110	982	0.280	11.6%	17	147	11.4%	25	220	0.953	9.2%	18	195
Bowel symptoms QoL score	3.7	(3.2)	1220	3.6	(3.4)	964	0.427	3.8	(3.2)	141	3.6	(3.1)	212	0.745	3.2	(3.3)	195

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 12 Vaginal and sexual symptoms at baseline (all PROSPECT participants)

Symptom	Primary RCT: RCT1 (*N* = 1266 questionnaires)			Primary cohort: CC1 (*N* = 997 questionnaires)			*p*-value	Secondary RCT: RCT2 (*N* = 148 questionnaires)			Secondary cohort: CC2 (*N* = 221 questionnaires)			*p*-value	Uterine/vault: CC3 (*N* = 202 questionnaires)		
Vaginal																	
ICIQ-VS score	22.3	(9.1)	1130	22.4	(9.3)	878	0.787	22.3	(9.3)	134	23.8	(9.6)	188	0.162	24.2	(10.1)	171
Vaginal symptoms QoL score	5.1	(3.1)	1220	5.2	(3.2)	952	0.344	5.3	(3.4)	139	5.4	(3.2)	204	0.811	5.3	(3.5)	187
Vagina too tight	1.7%	20	1193	2.8%	26	925	0.076	2.2%	3	139	5.6%	11	197	0.122	3.2%	6	185
Sexual																	
Sex life at present	37.7%	469	1243	38.6%	373	967	0.686	38.6%	56	145	29.9%	64	214	0.086	35.4%	69	195
Reason for no sex life																	
No partner	26.9%	208	774	27.9%	166	594	0.711	36.0%	32	89	27.3%	41	150	0.239	35.7%	45	126
Vaginal symptoms	4.0%	31	774	4.7%	28	594		1.1%	1	89	5.3%	8	150		3.2%	4	126
Prolapse symptoms	42.4%	328	774	41.8%	248	594		36.0%	32	89	38.7%	58	150		43.7%	55	126
Other reason	21.8%	169	774	19.5%	116	594		22.5%	20	89	24.7%	37	150		12.7%	16	126
Reason not given	4.9%	38	774	6.1%	36	594		4.5%	4	89	4.0%	6	150		4.8%	6	126
Dyspareunia	8.8%	57	646	9.3%	46	492	0.759	8.1%	6	74	15.5%	15	97	0.146	10.8%	10	93
ICI Sexual Matters score	23.1	(14.2)	639	23.4	(14.3)	485	0.744	25.4	(12.9)	73	24.4	(15.5)	95	0.668	23.3	(15.1)	89
Sex life QoL score	6.4	(3.4)	743	6.4	(3.2)	575	0.901	7.4	(2.7)	78	6.8	(3.3)	112	0.214	6.7	(3.4)	114

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); Dyspareunia at baseline: denominator includes number of women who were sexually active and those who did not have a sex life because of prolapse symptoms; *International Consultation on Incontinence vaginal symptoms score*, combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

had previously been repaired. The compartment of previous surgery was unknown in 60 women, who were therefore classified as having a first repair.

We identified a number of important demographic and clinical differences between women who were having a primary and a secondary repair. Those having a primary repair were, on average, 2.7 years older than those having a secondary procedure (59.4 years vs. 62.1; $p < 0.001$; see *Table 5*).

Among women who were having a primary repair, fewer had had a previous hysterectomy than those having a repeat repair (28% vs. 69%; $p < 0.001$; see *Table 5*), and in the repeat repair group, the previous hysterectomy was more likely to have been via the vaginal, rather than abdominal, route. Very few women who were having a primary repair had experienced a previous vault repair (2%), whereas this was more common for women who were having a second repair (13%; $p < 0.001$; see *Table 5*). Only 7% of women who were having their first repair had previously had continence surgery, whereas 15% of those having a second procedure had done so ($p < 0.001$; see *Table 5*).

Women who were having their first prolapse repair had a slightly lower (better) level of symptoms measured on the Pelvic Organ Prolapse Symptom scale (13.5) compared with those having repeat surgery (14.7; $p < 0.001$; see *Table 8*). This was reflected in a higher (better) score for the primary group on the generic QoL scale [EuroQol-5 Dimensions (EQ-5D) 0.71 vs. 0.67; $p = 0.001$; see *Table 5*]. Significantly more women who were having their first prolapse operation (64%) had a prolapse beyond the hymen (> 0 cm) than those (55%) having a repeat repair ($p = 0.001$; see *Table 7*).

Finally, more than three times as many women who were having a first repair were expected to require a concomitant vaginal hysterectomy (34% vs. 9%), and twice as many were expected to have concomitant continence surgery (12% vs. 6%), compared with those having a repeat repair, whereas women who were having a repeat repair were more likely to require a concomitant vault repair (25% vs. 18% for the primary group; see *Table 6*).

Summary

The women (both randomised and CC) enrolled in the PROSPECT Study represent 85% of the UK women who had prolapse surgery in the PROSPECT centres. We used strict definitions according to IUGA/ICS recommendations to categorise them and allocate them to clinically meaningful groups. In this chapter, we compared randomised and non-randomised women.

Summary of findings

The average age for a first prolapse repair was just < 60 years, with women who were having repeat (secondary) surgery being around 2.5 years older (see *Table 5*). Most women's babies had been delivered vaginally. Although the mean BMI was < 30 kg/m^2, 43 morbidly obese women with a BMI of ≥ 40 kg/m^2 did receive surgery.

Women who were having a repeat repair were more likely to have had a previous vaginal hysterectomy, vault repair or continence surgery. This difference in clinical characteristics justified our initial decision to conduct two separate trials among women who were having a first repair (primary) and a repeat repair (secondary).

Prolapse symptoms and measurements

Most women were expected to have surgery for an anterior vaginal wall prolapse (see *Table 6*). The majority of women had stage 2 prolapse, whereas around one-third had stage 3 or 4 (see *Table 7*). When prolapse was redefined as the leading edge beyond the hymen (> 0 cm on POP-Q), around 63% of women had a protruding prolapse: this was most common among women who were randomised in the Primary trial (67% compared with both the Primary CC (61%) and the Secondary women [52% (RCT2), 58% (CC2)].

Women had a high level of prolapse symptomatology, as shown by their POP-SSs, of around 14 out of a maximum score of 28 (see *Table 8*). The most common symptom was a feeling of something coming down (over 90%; see *Table 9*). Women who were having repeat surgery were less likely to have prolapse beyond the hymen (see *Table 7*) but their symptom score was, on average, one point higher (worse) than those having their first repair, and their prolapse-related QoL score was significantly worse (see *Table 8*).

Other clinical symptoms

Over three-quarters of women had UI, and this was slight or moderate in most cases (see *Table 10*). Nevertheless, at least one in five women had severe urine leakage, defined using the ICI-UI SF score of ≥ 13, and most of them had stress UI ('most or all of the time'). However, only around 10% of those with UI having a first repair, and 5% having a repeat repair, were expected to undergo continence surgery (see *Table 6*); on the other hand, 1 in 20, and 1 in 8, respectively, had already had previous continence surgery (see *Table 5*).

Around 1 in 10 women had bowel urgency or severe FI, and over one-third of women reported at least occasional faecal leakage, mostly passive (see *Table 11*). The pattern of bowel problems was remarkably similar in women who were having first or repeat prolapse surgery, and within these groups.

Just over one-third of the women were sexually active at baseline (see *Table 12*). Around 10% of them reported dyspareunia before surgery: as more women answered this question than the number professing to be sexually active, it can be inferred that some women may have refrained from intercourse because of dyspareunia or other prolapse symptoms. We allowed for this by including the women who were sexually inactive because of prolapse symptoms in the denominator for this analysis. Interestingly, the proportion with dyspareunia was similar in women who were having first or repeat prolapse surgery, around 10–15%.

In summary, there were no important clinical differences between women randomised in PROSPECT, and the comparable CC populations who were not randomised.

Strengths and weaknesses

PROSPECT is the most comprehensive study of women who were having prolapse surgery in the UK. The large number of women (over 3000), centres (35) and recruiting gynaecologists (70), and recruitment of 80% of their patients who had prolapse surgery, ensured that the findings are representative of the majority of general gynaecological practice within the NHS in the UK. The centres were a mix of secondary and tertiary referral hospitals.

We used a tightly defined classification of primary and secondary repair using international recommendations to separate our population of women. Within each group, there were few systematic differences between women who were randomised, and those who were not. On the other hand, there were clear clinical and demographic differences between women who were having a first or a repeat procedure, thus justifying our decision to analyse these groups of women in separate trials.

Our definition of secondary surgery was prespecified to refer to 'repeat surgery in the same compartment'. This resulted in some women who had a previous repair in another compartment being classified as 'primary'. Although we do not know the original denominator, we can calculate an approximation of the total number of women who were having any further prolapse surgery: dividing the number of women who were having any repeat repair ($n = 674$) by the number presenting for a first operation ($2474 - 276 = 2198$) suggests that the population rate of further surgery is 30.7%, very similar to that published by Olsen *et al.*[4] for further prolapse surgery in any compartment.

Conflict of interest

The study was not at risk of bias because it was publicly funded, and the investigators did not have personal or professional links with industry. The commercial companies which manufactured the mesh

and mesh kits did not provide any funding or material in kind (such as the supply of free materials) to the centres, the surgeons or the investigators.

Choice of validated outcome measures

We chose outcome measures for PROSPECT to reflect international standards[57] of reporting and ensure that the findings would be relevant to the needs of all groups that were likely to be affected by the findings, including patients, clinical staff and policy-makers. These outcomes were measured at baseline to provide values for later statistical adjustments. Our primary measure of prolapse symptoms was the subjective woman-reported prolapse symptom scale (Pelvic Organ Prolapse Symptom scale), developed and validated in a variety of populations for both research and in clinical practice.[27] This tool is relevant to women and, arguably, focused on the symptoms that led them to seek treatment.

We used validated instruments to measure secondary urinary and vaginal symptoms.[26] Similar short validated measures for bowel function were not available in the ICI suite of outcome measures when we started our study. We therefore adapted the questions used in the long ICIQ-Bowel Symptom instrument. We are currently validating them. In addition, we adapted some of these bowel function questions to approximate those advocated in the ROME consultation (see *Table 1*).

The objective assessment of prolapse stage was carried out using the standardised and internationally recognised POP-Q system.[27] Although the majority of women were classed as stage 2, based on the leading edge of the prolapse, some researchers have called into question whether or not this is an appropriate cut-off point for the diagnosis of prolapse. The mismatch between symptoms and objective findings is well recognised.[3,59,60] Based on this argument, Nygaard *et al.*[28] chose to define objective prolapse as leading edge beyond the hymen (> 0 cm) in a prolapse surgery trial. We have therefore used this cut-off point to dichotomise the ordinal POP-Q findings in the women who had individual measurements recorded at baseline (83% of all women).

Blinding of participants

Clinical baseline data were reported by women before randomisation using self-completed questionnaires. The objective assessment of prolapse stage before surgery was also carried out, as far as possible, by observers who did not have knowledge of the randomised operations, normally before a decision for surgery had been made.

Objective outcome measures

We were able to ascribe a prolapse stage to 93% of women at baseline, although only 83% had at least one recorded measurement on the POP-Q examination. It is difficult to explain why a small minority of women appeared not to have significant prolapse (stage 0 or 1). We can offer a number of suggestions. These measurements may have been recorded:

- without the use of provocation, such as Valsalva manoeuvre or coughing, *or*
- without the use of position and gravity to demonstrate the maximum descent, *or*
- at a time when the prolapse was not evident (e.g. in the morning), *or*
- in theatre under anaesthetic, *or*
- with a pessary in place, *or*
- incorrectly.

We did check that the patients' symptoms were bothersome (according to the Pelvic Organ Prolapse Symptom scale). These women clearly requested surgery, with which their gynaecologists concurred.

During the study we placed emphasis on the importance of accurate recording of stage and compartment using the POP-Q guideline.[27] We hope that demonstration of these few apparently anomalous women will improve clinical practice with respect to selection of women for prolapse surgery, and/or their better assessment.

Conclusions and further research

The wide inclusion criteria, minimal exclusion criteria and high recruitment rate have ensured that the women studied in PROSPECT are representative of those having prolapse surgery in the UK and the clinical practice of the gynaecologists who treat them. There were clear clinical and demographic differences between women who were having a first and a repeat repair, justifying our decision to study these groups in separate trials. However, within each trial, women who were and were not randomised were broadly similar. The findings of the randomised trials in PROSPECT will therefore be generalisable to the wider population of women with prolapse.

The findings in this chapter will serve as a benchmark for future research in women with prolapse. The clinical messages regarding symptoms and clinical practice may be helpful in improving prolapse management in the UK and internationally.

Chapter 4 Results: Primary trial (randomised controlled trial 1, comprehensive cohort 1)

This chapter describes the women who were having their first anterior or posterior prolapse repair, both those randomised (RCT1) and those who were not randomised but agreed to be followed up in the CC (CC1). The baseline characteristics of the women enrolled in RCT1 and CC1 have been described and compared in *Chapter 3*; by and large, the populations were similar.

The flow of women through the study is shown in the CONSORT diagram (*Figure 4*) in line with recommendations of CONSORT.[56]

The women received surgery in 35 centres across the UK (see *Table 4*). Although 1348 women were randomised in total, they are further subdivided according to the panel of operations against which they were randomised. Therefore, RCT1 consists of three strata: RCT1A, for which women were randomly allocated to any of the three options for this trial; RCT1B, for which women were randomised between standard repair with no mesh and synthetic mesh inlay; and RCT1C, for which women were randomised between no mesh and a biological graft inlay.

In this chapter, the data are presented according to the strata:

1. *Trial 1* Standard repair (no mesh) compared with synthetic mesh inlay [stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation)], *and*
2. *Trial 2* Standard repair (no mesh) compared with biological graft inlay [stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation)].

Because the analyses were carried out separately for each trial, some women in the 'no mesh' group from stratum 1A are included in the standard repair arm in both trial 1 and trial 2.

Baseline comparability of randomised groups

Women's characteristics at baseline

There were no important epidemiological or clinical differences between the randomised groups of women, including the EQ-5D-3L (trial 1, trial 2; *Table 13*) or between the randomised women in RCT1 and the non-randomised in CC1 (see *Table 13*). In this chapter, the data for the cohort women are provided in the outcome tables for comparison with the randomised groups but they have not been formally statistically compared.

The ages of the recruited women ranged from 24 to 90 years. The mean BMI was < 30 kg/m^2 for all groups of women but 10% had a BMI of > 35 kg/m^2. The majority of women were parous: only 1% had not had any deliveries. Most babies had been born by spontaneous vaginal delivery. All of the groups were comparable at baseline.

Regarding previous treatment, 13.1–17.5% were using a vaginal pessary, and 25.8–30.1% had seen a physiotherapist for prolapse symptoms, but rather fewer for UI; and around 1 in 10 had used drugs for UI. Regarding previous prolapse surgery, 8.2–12.9% had prior treatment, but these were all in the compartment opposite to the one now requiring repair. In terms of upper compartment procedures, 23.3–28.8% of women had a prior hysterectomy (more than half of those were via the abdominal route); and 5.4–7.2% had already had continence surgery.

Type of repair	Primary 1348																	
Stratum/ comparison	All 1348			Trial 1 865		Trial 2 735		RCT1A 762			RCT1B 358			RCT1C 228				
Treatment arm	Standard repair[a] 545	Synthetic mesh[b] 435	Biological graft[c] 368	Standard repair 430	Synthetic mesh 435	Standard repair 367	Biological graft 368	Standard repair 252	Synthetic mesh 255	Biological graft 255	Standard repair 178	Synthetic mesh 180		Standard repair 115	Biological graft 113			
Received surgery	537 (99%)	425 (98%)	363 (99%)	425 (99%)	425 (98%)	359 (98%)	363 (99%)	247	250	251	178	175		112	112			
• Standard repair	512 (95%)	60 (14%)	57 (16%)	403 (95%)	60 (14%)	342 (95%)	57 (16%)	233	28	35	170	32		109	22			
• Synthetic mesh	2 (0%)	341 (80%)	6 (2%)	2 (0%)	341 (80%)	1 (0%)	6 (2%)	1	209	5	1	132		0	1			
• Biological graft	2 (0%)	5 (1%)	294 (81%)	0 (0%)	5 (1%)	2 (1%)	294 (81%)	0	4	205	0	1		2	89			
• Mesh kit	2 (0%)	1 (0%)	0 (0%)	2 (0%)	1 (0%)	0 (0%)	0 (0%)	0	0	0	2	1		0	0			
• Other surgery[d]	19 (4%)	18 (4%)	6 (2%)	18 (4%)	18 (4%)	14 (4%)	6 (2%)	13	9	6	5	9		1	0			
No surgery	8 (1%)	10 (2%)	5 (1%)	5 (1%)	10 (2%)	8 (2%)	5 (1%)	5	5	4	0	5		3	1			
Baseline questionnaire	510 (94%)	414 (95%)	342 (93%)	409 (95%)	414 (95%)	340 (93%)	342 (93%)	239	239	241	170	175		101	101			
6-month questionnaire	504 (94%)	381 (90%)	335 (92%)	398 (93%)	381 (88%)	338 (92%)	335 (91%)	232	224	228	166	157		106	107			
Withdrawals within 6 months	0 (0%)	1 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0	1	1	0	0		0	0			
Deaths within 6 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0	0	0		0	0			
12-month short questionnaire	504 (94%)	389 (92%)	337 (93%)	395 (92%)	389 (89%)	342 (93%)	337 (92%)	233	226	230	162	163		109	107			
12-month long questionnaire	468 (87%)	362 (85%)	316 (87%)	368 (86%)	362 (83%)	319 (87%)	316 (86%)	219	212	214	149	150		100	102			
12-month clinic assessment	477 (89%)	374 (88%)	320 (88%)	381 (89%)	374 (86%)	319 (87%)	320 (87%)	223	217	221	158	157		96	99			
Withdrawals within 12 months	2 (0%)	4 (1%)	2 (1%)	2 (0%)	4 (1%)	1 (0%)	2 (1%)	1	4	2	1	0		0	0			
Deaths within 12 months	1 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0	0	1	1	0		0	0			
24-month questionnaire	445 (82%)	343 (79%)	300 (82%)	348 (81%)	343 (79%)	299 (81%)	300 (82%)	202	202	210	146	141		97	90			
Withdrawals within 24 months	13 (2%)	11 (3%)	5 (1%)	11 (3%)	11 (3%)	8 (2%)	5 (1%)	6	8	4	5	3		2	1			
Deaths within 24 months	2 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)	1 (0%)	1 (0%)	0	0	1	1	0		1	0			

FIGURE 4 CONSORT diagram for Primary trial. a, *Reasons for non-compliance with randomised allocation – standard*: no prolapse surgery (4); no anterior or posterior repair (14); mesh not required (0); mesh required (5); morbidity/surgical complications (0); patient decided did not want mesh post randomisation (0); theatre not informed/wrong information given (1); mesh not available (0); not enough theatre time (0); consultant not in theatre (0); no reason given for non-compliance (1). b, *Reasons for non-compliance with randomised allocation – synthetic*: no prolapse surgery (4); no anterior or posterior repair (14); mesh not required (17); mesh required (1); morbidity/surgical complications (17); patient decided did not want mesh post randomisation (5); theatre not informed/wrong information given (11); mesh not available (1); not enough theatre time (2); consultant not in theatre (1); no reason given for non-compliance (11). c, *Reasons for non-compliance with randomised allocation – biological*: no prolapse surgery (0); no anterior or posterior repair (7); mesh not required (13); mesh required (4); morbidity/surgical complications (7); patient decided did not want mesh post-randomisation (5); theatre not informed/wrong information given (10); mesh not available (7); not enough theatre time (8); consultant not in theatre (2); no reason given for non-compliance (6). d, '*Other surgery*' includes tape for UI, vaginal hysterectomy or suspension, cervical amputation, vault repair without anterior or posterior repair.

TABLE 13 Baseline characteristics of participants: Primary trial

Baseline characteristic	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
	Standard repair ($N = 430$ women)			Synthetic mesh ($N = 435$ women)			Standard repair ($N = 367$ women)			Biological graft ($N = 368$ women)			CC1 ($N = 1126$ women)		
Age (years)	59.8	(10.1)	430	59.5	(10.4)	435	59.7	(10.4)	367	58.9	(10.5)	368	59.4	(11.6)	1126
Parity (mean)	2.6	(1.1)	429	2.7	(1.2)	433	2.6	(1.1)	367	2.7	(1.1)	367	2.5	(1.1)	1115
Parity (median)	2	(0–8)	429	2	(0–9)	433	2	(0–8)	367	2	(1–7)	367	2	(0–12)	1115
BMI (kg/m^2) (mean)	28.6	(4.9)	387	28.8	(4.9)	386	28.5	(4.8)	325	28.5	(4.6)	326	28.2	(4.8)	1023
BMI (kg/m^2) (median)	28	(19–45)	387	28	(19–49)	386	28	(18–45)	325	28	(16–42)	326	28	(17–50)	1023
Delivery mode history															
Spontaneous vaginal delivery	2.2	(1.3)	421	2.4	(1.3)	425	2.2	(1.3)	358	2.2	(1.2)	360	2.2	(1.2)	1085
Forceps	0.2	(0.5)	421	0.2	(0.5)	425	0.3	(0.5)	358	0.2	(0.5)	360	0.2	(0.4)	1085
Breech	0.0	(0.2)	421	0.0	(0.2)	425	0.0	(0.2)	358	0.0	(0.2)	360	0.0	(0.2)	1085
Elective caesarean	0.1	(0.3)	421	0.1	(0.2)	425	0.1	(0.3)	358	0.0	(0.2)	360	0.1	(0.2)	1085
Emergency caesarean	0.0	(0.3)	421	0.1	(0.2)	425	0.0	(0.2)	358	0.0	(0.2)	360	0.0	(0.2)	1085
Vacuum delivery	0.0	(0.1)	421	0.0	(0.1)	425	0.0	(0.2)	358	0.0	(0.2)	360	0.0	(0.1)	1085
EQ-5D-3L															
Score	0.72	(0.24)	398	0.71	(0.23)	406	0.72	(0.24)	330	0.71	(0.25)	329	0.71	(0.25)	964
Previous conservative treatment															
Current vaginal pessary	14.7%	63	429	13.1%	57	434	17.5%	64	366	14.0%	51	364	11.8%	131	1111
Physiotherapy for prolapse	27.0%	116	429	30.1%	130	432	27.6%	101	366	25.8%	94	365	30.3%	335	1105
Physiotherapy for UI	15.5%	66	427	17.6%	76	432	15.1%	55	365	15.6%	57	365	17.7%	196	1107
Drugs for UI	8.9%	38	428	12.1%	52	430	9.3%	34	365	10.7%	39	363	11.8%	130	1100

continued

TABLE 13 Baseline characteristics of participants: Primary trial (*continued*)

Baseline characteristic	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological						CC1 (*N* = 1126 women)		
	Standard repair (*N* = 430 women)			Synthetic mesh (*N* = 435 women)			Standard repair (*N* = 367 women)			Biological graft (*N* = 368 women)					
Previous surgery															
Previous prolapse repair	11.4%	49	430	12.9%	56	435	10.1%	37	367	8.2%	30	368	12.2%	137	1126
Anterior	4.4%	19	430	7.1%	31	435	4.1%	15	367	3.8%	14	368	5.0%	56	1126
Posterior	4.7%	20	430	3.7%	16	435	4.1%	15	367	1.1%	4	368	3.6%	40	1126
Anterior and posterior	0.0%	0	430	0.0%	0	435	0.0%	0	367	0.0%	0	368	0.0%	0	1126
Vault	2.1%	9	430	1.6%	7	435	1.9%	7	367	1.1%	4	368	2.6%	29	1126
Unknown compartment	1.6%	7	430	1.4%	6	435	1.4%	5	367	2.2%	8	368	2.3%	26	1126
Hysterectomy	23.3%	100	430	28.7%	125	435	25.1%	92	367	28.8%	106	368	29.8%	336	1126
Vaginal	7.0%	30	430	12.2%	53	435	7.9%	29	367	10.1%	37	368	10.7%	121	1126
Cervical amputation	2.3%	10	430	1.6%	7	435	2.2%	8	367	1.9%	7	368	2.7%	30	1126
Abdominal	16.3%	70	430	16.3%	71	435	17.2%	63	367	18.8%	69	368	18.7%	210	1126
Continence surgery	7.2%	31	429	6.3%	27	431	5.8%	21	365	5.4%	20	367	7.7%	86	1111

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Preoperative prolapse measurements

Women in the randomised groups in each trial were comparable in terms of the maximum descent of the three different prolapse compartments. Using qualitative descriptions of prolapse stage to supplement missing POP-Q data, > 98% of the women had prolapse stage 2 or greater before surgery. For the women who had a quantitative score measured using the POP-Q system, about two-thirds were found to have the leading edge of the prolapse outside the hymen (> 0 cm). *Table 14* shows the level of prolapse in the individual compartments.

Prolapse symptoms at baseline

Women had noticed symptoms of prolapse for a mean of 3.3–3.8 years, and had been bothered for 2.4–2.8 years before surgery (*Table 15*). The Pelvic Organ Prolapse Symptom scale is composed of seven individual prolapse symptoms (each scored from 0 to 4, where 0 is 'never' and 4 is 'all the time'; see *Chapter 2*). The mean POP-SS ranged from 13.7 to 13.8 out of a maximum score of 28. Almost all women (over 99%) were deemed to be symptomatic using the criterion of scoring at least 1 on the Pelvic Organ Prolapse Symptom scale (see *Table 15*). The most common symptom was 'a feeling of something coming down from or in the vagina', and over 90% of women reported this symptom at least occasionally, whereas about two-thirds had a visible prolapse outside the hymen (see *Table 14*).

As well as the women in each trial being comparable at baseline for the overall score, there were no systematic differences in any individual prolapse symptoms or other measures of the effect of prolapse on QoL or in modifying women's behaviour to ameliorate the effects of prolapse.

Urinary symptoms at baseline

The urinary symptoms reported by women were captured using a variety of validated questionnaires and scales from the ICI Modular Questionnaire suite[26] (*Table 16*). Around four in five women had at least some urinary leakage, and this was severe for one in five.

There were no systematic differences between the women in either trial but urinary symptoms were common in women with prolapse.

Bowel symptoms at baseline

We captured a variety of bowel symptoms (*Table 17*). There were no systematic differences between the randomised groups in terms of frequency of bowel movements, constipation, bowel urgency or FI, or in the effect bowel symptoms had on QoL. Around 30% of the women had constipation (using the ROME[30] criteria) and over one-third reported FI at least occasionally.

Vaginal and sexual symptoms at baseline

We used the validated ICIQ-VS and the ICI Sexual Matters instruments to capture aspects of vaginal and sexual function.[26] Between 59.9% and 64.9% of women were not sexually active (*Table 18*); around one-quarter of these women did not have sexually active partners, and the most common reason in the remainder was 'due to their prolapse symptoms'. Around 6.6–11.4% of women who answered the question reported pain with intercourse (dyspareunia). There were no systematic differences between the randomised groups in terms of these clinical measures at baseline.

Surgery planned before surgery and actually received during surgery

Planned operations

The most common operation (anticipated for three-quarters of women) was anterior repair, with just over half of the women planning to have a posterior repair: of these women, around 30% were having a joint procedure (*Table 19*). Concomitant surgery included about one-third of the women who were thought to need a vaginal hysterectomy, and a further 12.6–18.2% requiring a vault repair. Finally, 9.5–11.7% were thought to require a continence procedure. There were no differences between the women in different arms of the study (see *Table 19*).

TABLE 14 Preoperative objective measures of prolapse: Primary trial

POP-Q measurement/stage	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological						CC1 (*N* = 1126 women)		
	Standard repair (*N* = 430 women)			Synthetic mesh (*N* = 435 women)			Standard repair (*N* = 367 women)			Biological graft (*N* = 368 women)					
POP-Q measurement (cm)															
Ba (anterior edge)	0.6	(2.2)	382	0.5	(2.1)	380	0.4	(2.1)	328	0.4	(2.1)	327	0.4	(2.1)	860
C (cervix/vault)	–3.5	(3.6)	359	–3.5	(3.3)	352	–3.4	(3.3)	314	–3.2	(3.3)	300	–3.2	(3.3)	812
Bp (posterior edge)	–0.3	(2.0)	380	–0.5	(1.9)	380	–0.4	(1.8)	327	–0.3	(1.8)	325	–0.5	(1.8)	855
TVL	8.5	(1.4)	357	8.5	(1.7)	359	8.3	(1.5)	292	8.2	(1.7)	292	8.5	(1.8)	809
Overall POP-Q stage															
0	0.2%	1	413	0.0%	0	421	0.3%	1	352	0.3%	1	354	0.0%	0	997
1	0.7%	3	413	1.7%	7	421	0.6%	2	352	0.6%	2	354	2.0%	20	997
2	55.4%	229	413	56.1%	236	421	61.1%	215	352	53.1%	188	354	62.0%	618	997
3	39.7%	164	413	39.9%	168	421	35.5%	125	352	44.9%	159	354	34.3%	342	997
4	3.9%	16	413	2.4%	10	421	2.6%	9	352	1.1%	4	354	1.7%	17	997
2b, 3 or 4	*65.6%*	*259*	*395*	*68.8%*	*273*	*397*	*62.7%*	*210*	*335*	*69.3%*	*235*	*339*	*60.6%*	*536*	*884*

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

TABLE 15 Prolapse symptoms at baseline: Primary trial

Symptom	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
	Standard repair (*N* = 409 women)			Synthetic mesh (*N* = 414 women)			Standard repair (*N* = 340 women)			Biological graft (*N* = 342 women)			CC1 (*N* = 997 women)		
POP-SS at baseline	13.7	(6.1)	409	13.7	(5.6)	414	13.8	(6.0)	340	13.7	(5.9)	342	13.3	(5.8)	995
Individual prolapse															
SCD any	92.4%	378	409	93.0%	385	414	92.4%	314	340	93.0%	318	342	93.9%	934	995
SCD freq.	64.5%	264	409	66.9%	277	414	67.1%	228	340	65.5%	224	342	66.5%	662	995
Pain any	80.4%	329	409	79.0%	327	414	82.4%	280	340	81.0%	277	342	81.6%	812	995
Pain freq.	32.8%	134	409	34.3%	142	414	33.2%	113	340	36.5%	125	342	36.4%	362	995
Abdo. any	79.2%	324	409	83.1%	344	414	78.8%	268	340	80.7%	276	342	79.2%	788	995
Abdo. freq.	33.3%	136	409	35.7%	148	414	31.8%	108	340	33.6%	115	342	33.4%	332	995
Back any	72.9%	298	409	74.6%	309	414	73.8%	251	340	70.5%	241	342	68.6%	683	995
Back freq.	28.1%	115	409	30.4%	126	414	28.5%	97	340	31.0%	106	342	25.8%	257	995
Strain blad. any	70.4%	288	409	72.0%	298	414	69.1%	235	340	73.4%	251	342	69.5%	692	995
Strain blad. freq.	29.8%	122	409	28.7%	119	414	29.1%	99	340	28.7%	98	342	26.1%	260	995
Blad. not empty any	80.4%	329	409	83.1%	344	414	79.4%	270	340	83.6%	286	342	83.0%	826	995
Blad. not empty freq.	38.6%	158	409	37.7%	156	414	38.8%	132	340	38.0%	130	342	35.7%	355	995
Bowel not empty any	81.4%	333	409	82.4%	341	414	83.5%	284	340	82.5%	282	342	79.0%	786	995
Bowel not empty freq.	37.9%	155	409	34.8%	144	414	38.8%	132	340	38.0%	130	342	30.8%	306	995
Other measures of prolapse symptoms															
Duration of symptoms (years)	3.8	(5.9)	395	3.3	(4.5)	392	3.8	(5.4)	331	3.7	(4.6)	331	3.6	(5.0)	948
Duration of bother (years)	2.8	(4.9)	384	2.4	(3.8)	380	2.5	(3.7)	322	2.7	(3.7)	310	2.5	(3.4)	916
Symptomatic	100.0%	409	409	99.5%	412	414	100.0%	340	340	99.1%	339	342	99.6%	991	995
Prolapse-related QoL score	6.5	(2.8)	408	6.6	(2.7)	406	6.7	(2.7)	338	6.6	(2.8)	338	6.7	(2.7)	969

continued

TABLE 15 Prolapse symptoms at baseline: Primary trial (*continued*)

Symptom	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
	Standard repair (*N* = 409 women)			Synthetic mesh (*N* = 414 women)			Standard repair (*N* = 340 women)			Biological graft (*N* = 342 women)			CC1 (*N* = 997 women)		
Actions necessitated by prolapse symptoms															
Fingers to ease discomfort	23.6%	95	402	19.7%	80	406	23.0%	77	335	19.5%	66	339	19.4%	189	972
Extra hygiene measures	54.0%	217	402	51.5%	208	404	51.5%	172	334	49.4%	165	334	47.9%	465	970
Fingers to help empty bladder	4.5%	18	403	2.9%	12	409	3.6%	12	336	4.5%	15	337	4.9%	48	976
Fingers to help empty bowel	11.1%	45	407	11.2%	45	401	11.8%	40	339	9.9%	33	335	11.2%	109	972
Digital evacuation of bowel	6.9%	28	407	8.0%	32	401	7.4%	25	337	7.4%	25	338	8.4%	82	977

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome; *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

Prolapse symptoms

Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time.; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely?' (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad.* any: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.

Bowel symptoms

Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

TABLE 16 Urinary symptoms at baseline: Primary trial

Symptom	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
	Standard repair (*N* = 409 women)			Synthetic mesh (*N* = 414 women)			Standard repair (*N* = 340 women)			Biological graft (*N* = 342 women)			CC1 (*N* = 997 women)		
Any incontinence	76.8%	314	409	76.5%	315	412	76.2%	259	340	78.0%	266	341	76.1%	756	994
ICIQ-UI-SF score	7.0	(5.5)	403	7.1	(5.8)	408	6.9	(5.5)	337	7.4	(5.8)	339	7.2	(5.8)	974
Severe incontinence	19.4%	78	403	21.1%	86	408	19.3%	65	337	21.8%	74	339	22.0%	214	974
Incontinence-related QoL score	3.5	(3.3)	394	3.6	(3.5)	402	3.5	(3.4)	326	3.7	(3.4)	330	3.7	(3.5)	956
Stress UI	23.6%	84	356	24.1%	90	374	25.3%	74	293	24.9%	76	305	25.0%	220	881
Urgency UI	8.9%	36	406	10.0%	41	411	9.2%	31	338	10.7%	36	338	10.6%	104	982
Overactive bladder	5.3%	21	399	5.1%	21	409	3.9%	13	333	8.1%	27	335	5.6%	55	977
ICIQ-FLUTS filling score	5.1	(2.9)	397	5.3	(2.9)	404	5.2	(2.9)	331	5.5	(3.0)	334	5.3	(2.9)	970
ICIQ-FLUTS voiding score	3.2	(2.7)	402	3.1	(2.5)	406	3.1	(2.6)	334	3.1	(2.6)	336	3.1	(2.6)	975
ICIQ-FLUTS incontinence score	6.1	(4.1)	350	6.0	(4.2)	371	6.2	(4.1)	291	6.4	(4.2)	300	6.1	(4.3)	858

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

TABLE 17 Bowel symptoms at baseline: Primary trial

Symptom	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological						CC1 (*N* = 997 women)		
	Standard repair (*N* = 409 women)			Synthetic mesh (*N* = 414 women)			Standard repair (*N* = 340 women)			Biological graft (*N* = 342 women)					
Bowel frequency															
> 3 times a day	5.9%	24	408	4.9%	20	405	7.4%	25	339	6.2%	21	337	5.0%	49	977
1–3 times a day	33.3%	136	408	36.3%	147	405	32.2%	109	339	31.8%	107	337	36.2%	354	977
About once a day	40.2%	164	408	37.5%	152	405	39.5%	134	339	42.1%	142	337	40.4%	395	977
Once every 2–3 days	16.4%	67	408	17.5%	71	405	17.1%	58	339	18.4%	62	337	16.6%	162	977
Weekly or less	4.2%	17	408	3.7%	15	405	3.8%	13	339	1.5%	5	337	1.7%	17	977
Constipation	29.0%	117	404	27.1%	108	399	32.0%	108	338	29.1%	97	333	24.6%	239	970
Bowel urgency	11.7%	48	409	9.9%	40	405	11.8%	40	339	15.0%	51	339	10.8%	106	985
FI (any)	34.3%	140	408	34.0%	138	406	33.4%	113	338	35.8%	121	338	33.4%	328	982
Passive FI	72.1%	101	140	77.4%	106	137	74.3%	84	113	66.9%	81	121	75.8%	248	327
Active FI	27.9%	39	140	22.6%	31	137	25.7%	29	113	33.1%	40	121	24.2%	79	327
Severe FI	12.5%	51	408	11.3%	46	406	10.7%	36	338	15.4%	52	338	11.2%	110	982
Bowel symptoms QoL score	3.8	(3.2)	396	3.6	(3.2)	393	3.8	(3.2)	328	3.8	(3.3)	332	3.6	(3.4)	964

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 18 Vaginal and sexual symptoms at baseline: Primary trial

Symptom	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
	Standard repair (*N* = 409 women)			Synthetic mesh (*N* = 414 women)			Standard repair (*N* = 340 women)			Biological graft (*N* = 342 women)			CC1 (*N* = 997 women)		
Vaginal															
ICIQ-VS score	22.1	(9.0)	367	22.2	(9.4)	365	21.7	(8.7)	302	22.8	(9.1)	307	22.4	(9.3)	878
Vaginal symptoms QoL score	4.9	(3.1)	396	5.1	(3.1)	396	5.0	(3.1)	328	5.2	(3.2)	329	5.2	(3.2)	952
Vagina too tight	1.8%	7	387	1.6%	6	385	2.2%	7	323	1.8%	6	327	2.8%	26	925
Sexual															
Sex life at present (yes)	37.3%	152	407	37.1%	148	399	35.1%	119	339	40.1%	135	337	38.6%	373	967
Reason for no sex life															
No partner	23.5%	60	255	31.1%	78	251	24.1%	53	220	25.2%	51	202	27.9%	166	594
Vaginal symptoms	5.1%	13	255	2.0%	5	251	5.9%	13	220	4.5%	9	202	4.7%	28	594
Prolapse symptoms	42.7%	109	255	39.4%	99	251	43.2%	95	220	48.0%	97	202	41.8%	248	594
Other reason	23.9%	61	255	21.9%	55	251	22.3%	49	220	17.3%	35	202	19.5%	116	594
Reason not given	4.7%	12	255	5.6%	14	251	4.5%	10	220	5.0%	10	202	6.1%	36	594
Dyspareunia	8.3%	18	217	6.6%	13	197	11.4%	20	175	11.3%	21	186	9.3%	46	492
ICI Sexual Matters score	22.4	(14.4)	215	23.5	(13.3)	195	23.3	(15.2)	173	23.5	(14.7)	183	23.4	(14.3)	485
Sex life QoL score	6.4	(3.4)	244	6.5	(3.3)	231	6.4	(3.5)	195	6.5	(3.4)	217	6.4	(3.2)	575

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *Dyspareunia at baseline*: denominator includes number of women who were sexually active and those who did not have a sex life because of prolapse symptoms; *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

TABLE 19 Planned prolapse procedure and surgery actually performed: Primary trial

	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
Type of surgery	**Standard repair**			**Synthetic mesh**			**Standard repair**			**Biological graft**			**CC1 (*N* = 1126)**		
Number of women	*N* = 430			*N* = 435			*N* = 367			*N* = 368					
Planned prolapse procedure															
Anterior repair	48.6%	209	430	48.5%	211	435	40.9%	150	367	40.5%	149	368	44.5%	501	1126
Posterior repair	25.8%	111	430	25.5%	111	435	25.3%	93	367	26.6%	98	368	26.8%	302	1126
Anterior and posterior repair	25.6%	110	430	26.0%	113	435	33.8%	124	367	32.9%	121	368	28.7%	323	1126
Upper compartment repair only	0.0%	0	430	0.0%	0	435	0.0%	0	367	0.0%	0	368	0.0%	0	1126
Planned concomitant prolapse procedure															
Vaginal hysterectomy	35.8%	154	430	32.6%	142	435	36.5%	134	367	33.4%	123	368	32.7%	368	1126
Cervical amputation	1.9%	8	430	2.1%	9	435	1.6%	6	367	1.4%	5	368	1.4%	16	1126
Abdominal hysterectomy	0.2%	1	430	0.0%	0	435	0.0%	0	367	0.0%	0	368	0.4%	4	1126
Vault repair	12.6%	54	430	15.6%	68	435	16.6%	61	367	18.2%	67	368	20.9%	235	1126
Continence procedure	9.5%	41	430	10.3%	45	435	11.7%	43	367	11.4%	42	368	13.3%	150	1126
Number of women	*N* = 425			*N* = 425			*N* = 359			*N* = 363			*N* = 1104		
Surgery actually performed *Actual prolapse procedure*															
Anterior repair only	43.3%	184	425	44.0%	187	425	36.8%	132	359	36.4%	132	363	40.8%	450	1104
Posterior repair only	29.4%	125	425	29.9%	127	425	28.7%	103	359	32.2%	117	363	27.6%	305	1104
Anterior and posterior repair	23.1%	98	425	21.9%	93	425	30.6%	110	359	29.8%	108	363	25.5%	282	1104
Neither	4.2%	18	425	4.2%	18	425	3.9%	14	359	1.7%	6	363	6.1%	67	1104

	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological								
Type of surgery	Standard repair			Synthetic mesh			Standard repair			Biological graft			CC1 (*N* = 1126)		
Concomitant prolapse procedure															
Vaginal hysterectomy	31.8%	135	425	24.2%	103	425	31.2%	112	359	26.2%	95	363	29.8%	329	1104
Abdominal hysterectomy	0.0%	0	425	0.0%	0	425	0.0%	0	359	0.3%	1	363	0.4%	4	1104
Cervical amputation	2.1%	9	425	2.8%	12	425	2.2%	8	359	2.5%	9	363	0.7%	8	1104
Uterine suspension	4.7%	20	425	3.1%	13	425	4.5%	16	359	2.2%	8	363	5.0%	55	1104
Vault repair	11.5%	49	425	10.1%	43	425	10.9%	39	359	11.3%	41	363	13.5%	149	1104
Continence procedure	10.1%	43	425	10.6%	45	425	9.7%	35	359	12.1%	44	363	12.2%	135	1104

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Surgeons could use any mesh, graft or mesh kit, providing that any synthetic mesh was monofilament macroporous polypropylene and mesh inlays were secured with peripheral sutures.

In line with expectations, most women received the surgery planned. Twenty-three women did not receive surgery at all; reasons were being unfit for surgery, change of patient's mind, surgeon finding that the prolapse surgery was unnecessary, etc. (see *Figure 4*). Forty-three women did not have either an anterior or a posterior repair once anaesthetised because the surgeon did not deem it necessary for clinical reasons, and therefore they were unable to receive their randomised allocation (see *Figure 4*).

Surgery actually received

In both trials, more women had a vaginal hysterectomy in the standard arms than in the intervention arms, but this was not significant. It is possible that knowledge of the allocated intervention influenced the surgery actually performed. However, overall there were no substantial differences between the groups in the panel of operations carried out.

Compliance with randomised allocation

In addition to women who did not have any prolapse surgery ($N = 23$; see *Figure 4*) or did not require either an anterior or posterior repair ($N = 43$), and therefore could not receive their randomised allocation, six women who were randomised to standard repair received mesh ($N = 2$), graft ($N = 2$) or mesh kit ($N = 2$); 66 women who were randomised to synthetic mesh did not receive any ($N = 60$) or received a biological graft ($N = 5$) or mesh kit ($N = 1$); and 63 women who were randomised to biological graft did not receive it ($N = 57$) or received synthetic mesh ($N = 6$). In some cases, the reason for these protocol deviations were as a result of the appropriate mesh not being available in theatre or failure to inform the theatre staff in good time.

In trial 1, more women failed to receive their allocated (randomised) intervention in the synthetic mesh arm than in the control standard arm because of a clinical decision by the surgeon that mesh was not required, or because of morbidity or complications. Similarly in trial 2, more women did not receive their allocated biological graft than a standard repair because the surgeon decided that graft was or was not indicated and due to morbidity (see *Figure 4*).

Surgical characteristics and protocols

The majority of the operations were carried out by consultant gynaecological surgeons or specialty (staff grade) doctors (*Table 20*). Between 18.8% (synthetic mesh arm) and 30.5% (standard repair arm of trial 2) were undertaken by a junior doctor, but in those cases nearly 90% were supervised by a consultant. However, consultants were more likely to operate on women randomised to mesh or graft than standard repair. Around 80% of the women had a general anaesthetic, with no systematic differences between the groups.

Duration of surgery was significantly longer in the mesh group (by 5.9 minutes), but not significantly longer in the graft group (3.6 minutes) (*Table 21*). Blood loss was higher in the mesh group but not significantly so in the graft group compared with standard repair. The mean length of stay ranged from 2.4 to 2.9 days, with no differences between the randomised groups. This time included any preoperative days if the women were admitted a day before surgery.

Outcomes

The outcomes are compared between women within each of trial 1 and trial 2. The data for the equivalent outcomes for the cohort women are provided for comparison only but are not formally statistically compared with either trial.

TABLE 20 Description of surgical characteristics and protocols: Primary trial

Surgical characteristic	Trial 1: standard vs. synthetic						Trial 2: standard vs. biological						CC1 (*N* = 1102 women)		
	Standard repair (*N* = 425 women)			Synthetic mesh (*N* = 425 women)			Standard repair (*N* = 359 women)			Biological graft (*N* = 363 women)					
Grade of gynaecologist															
Consultant	70.6%	300	425	78.6%	331	421	59.4%	212	357	68.0%	247	363	70.8%	777	1098
Specialty doctor	7.1%	30	425	2.6%	11	421	10.1%	36	357	7.2%	26	363	12.9%	142	1098
Specialty doctor supervised	69.2%	18	26	80.0%	8	10	76.7%	23	30	83.3%	20	24	69.4%	84	121
Registrar/junior	22.4%	95	425	18.8%	79	421	30.5%	109	357	24.8%	90	363	16.3%	179	1098
Registrar/junior supervised	87.6%	78	89	89.7%	70	78	87.5%	91	104	89.7%	78	87	82.9%	141	170
Prophylactic antibiotic	92.4%	387	419	96.9%	409	422	91.8%	325	354	97.2%	351	361	95.5%	1016	1064
Type of anaesthetic															
General	80.0%	340	425	78.5%	332	423	84.9%	304	358	87.1%	316	363	84.8%	924	1090
Spinal	20.7%	88	425	22.9%	97	423	15.6%	56	358	15.2%	55	363	16.3%	178	1090
Local	10.8%	46	425	11.8%	50	423	8.7%	31	358	6.3%	23	363	14.0%	153	1090
Duration (minutes)	78.3	(34.6)	412	84.2	(32.0)	412	84.4	(41.6)	352	88.0	(38.6)	355	82.7	(37.0)	1052
Estimated blood loss (ml)	132.7	(132.4)	394	160.6	(152.7)	387	135.7	(145.7)	331	146.3	(114.0)	326	138.6	(158.2)	974
Vaginal pack inserted	81.4%	341	419	86.9%	353	406	83.1%	294	354	88.8%	317	357	74.8%	796	1064
Catheter inserted	91.7%	387	422	96.7%	405	419	91.3%	327	358	96.1%	349	363	93.4%	1020	1092
Suprapubic	1.8%	7	387	0.5%	2	404	1.8%	6	327	1.4%	5	349	0.3%	3	1016
Urethral	98.2%	380	387	99.0%	400	404	97.9%	320	327	98.3%	343	349	99.7%	1013	1016
Both	0.0%	0	387	0.5%	2	404	0.3%	1	327	0.3%	1	349	0.0%	0	1016
Length of stay (days)	2.4	(1.5)	423	2.6	(1.5)	419	2.6	(1.6)	356	2.9	(2.7)	363	2.3	(1.6)	1092

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

TABLE 21 Comparison of surgical characteristics (women who received surgery only): Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft												
Surgical characteristic	Standard (*N* = 425 women)			Synthetic (*N* = 425 women)			Effect size	95% CI	*p*-value	Standard (*N* = 359 women)			Biological (*N* = 363 women)			Effect size	95% CI	*p*-value	CC1 (*N* = 1104 women)		
Duration (minutes)	78.3	(34.6)	412	84.2	(32.0)	412	5.91	2.05 to 9.76	0.003	84.4	(41.6)	352	88.0	(38.6)	355	4.29	–0.05 to 8.62	0.052	82.7	(37.0)	1052
Blood loss (ml)	132.7	(132.4)	394	160.6	(152.7)	387	28.1	9.5 to 46.8	0.003	135.7	(145.7)	331	146.3	(114.0)	326	13.5	–4.3 to 31.30	0.138	138.6	(158.2)	974
Length of stay	2.4	(1.5)	423	2.6	(1.5)	419	0.11	–0.06 to 0.27	0.218	2.6	(1.6)	356	2.9	(2.7)	363	0.26	–0.03 to 0.56	0.081	2.3	(1.6)	1092

Continuous variables are presented as 'mean (SD) *N*'.

Serious and related adverse effects in first and second years

The diagnoses in *Table 22* are confined to those that met our definition of 'serious' (see *Chapter 2*). An adverse effect (AE) was defined as 'serious' (SAE) if it was related to prolapse surgery and resulted in death; was life-threatening; required hospitalisation or prolongation of an existing admission; resulted in significant disability/incapacity; or was otherwise considered medically significant by the investigator. If it did not meet the requirement for 'serious' then it was classed as 'other'.

Serious non-mesh adverse effects

The proportion of women reporting a serious adverse effect related to prolapse surgery but not mesh-related ranged from 6.3% to 9.8% in the first year, and 0.9% to 1.4% in the second year (*Table 22*). There was no statistically significant difference between the randomised groups in either trial and the rates were similar to those observed in the cohort. Individual serious effects were rare, the most common being infection, pain and urinary retention, all of which are common after gynaecological surgery, generally of short duration and easily treated. The data from the cohort women were similar.

Other related adverse effects in first and second years

The pattern for other (non-serious) adverse effects was very similar in both trials (*Table 23*). The overall number of effects was similar, and there were no statistically significant differences between the randomised groups in either trial.

Prolapse symptoms at 6 months, 1 year and 2 years

The women's report of prolapse symptoms, measured using the Pelvic Organ Prolapse Symptom scale, was less than half of the preoperative level (mean score before surgery 13.7/28; at 6 months 5.0/28; at 1 year 5.4/28; at 2 years 5.2/28) and the improvement remained at 2 years (*Tables 24* and *25*). There were no statistically significant differences between the randomised groups in either trial 1 or trial 2 at any time point.

Specifically the primary outcome was the POP-SS at 1 year (see *Table 24*).

1. In trial 1, the MD in the POP-SSs for standard repair (5.4, SD 5.5) compared with synthetic mesh inlay (5.5, SD 5.1), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), was MD 0.00 (95% CI –0.70 to 0.71).
2. In trial 2, the MD for standard repair (5.5, SD 5.6) compared with biological graft (5.6, SD 5.6), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), was MD –0.15, 95% CI –0.93 to 0.63.

At 2 years, the POP-SSs remained relatively stable, still with no difference between the groups (see *Table 24*).

1. In trial 1, the MD in the POP-SSs for standard repair (4.9, SD 5.1) compared with synthetic mesh inlay (5.3, SD 5.1), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation) was MD 0.32, 95% CI –0.39 to 1.03.
2. In trial 2, the MD for standard repair (4.9, SD 5.1) compared with biological graft (5.5, SD 5.7), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation) was MD 0.32, 95% CI –0.48 to 1.12.

The lack of difference between the groups was supported by (see *Tables 24* and *25*):

- data from individual prolapse symptoms (whether measured as 'any' or occurring 'most or all of the time')

TABLE 22 Serious and related adverse effects within first and second years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									Cohort		
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Intraoperative complications																					
Number of women at 1 year	*N* = 430			*N* = 435						*N* = 367			*N* = 368						*N* = 1126		
Injury to organs	0.2%	1	430	0.7%	3	435	3.05	0.32 to 28.83	0.330	0.3%	1	367	0.5%	2	368	1.97	0.18 to 21.63	0.578	0.1%	1	1126
Excess blood loss	0.5%	2	430	0.9%	4	435	2.12	0.39 to 11.41	0.380	0.3%	1	367	0.3%	1	368	1.02	0.06 to 16.23	0.987	0.2%	2	1126
Blood transfusion	0.7%	3	430	0.2%	1	435	0.32	0.03 to 3.03	0.319	0.5%	2	367	0.3%	1	368	0.52	0.05 to 5.70	0.595	0.5%	6	1126
Anaesthetic complications	0.2%	1	430	0.0%	0	435	N/A	N/A	N/A	0.3%	1	367	0.5%	2	368	1.99	0.18 to 21.82	0.573	0.6%	7	1126
Death	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Serious adverse effects in first year																					
Thrombosis	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.3%	1	368	N/A	N/A	N/A	0.1%	1	1126
Infection	3.0%	13	430	3.0%	13	435	0.98	0.46 to 2.08	0.957	2.2%	8	367	3.0%	11	368	1.35	0.55 to 3.32	0.508	2.54%	28	1126
Pain	2.3%	10	430	2.8%	12	435	1.18	0.542 to 2.69	0.697	1.4%	5	367	1.9%	7	368	1.43	0.47 to 4.42	0.529	1.4%	16	1126
Urinary retention	2.3%	10	430	1.1%	5	435	0.48	0.17 to 1.40	0.180	2.7%	10	367	2.2%	8	368	0.81	0.32 to 2.01	0.644	1.2%	13	1126
Bowel obstruction	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Constipation	0.2%	1	430	0.2%	1	435	0.99	0.06 to 15.66	0.992	0.3%	1	367	0.5%	2	368	2.02	0.18 to 22.07	0.565	0.4%	4	1126

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									Cohort		
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Excess blood loss	1.4%	6	430	1.8%	8	435	1.33	0.47 to 3.80	0.588	0.5%	2	367	0.3%	1	368	0.52	0.05 to 5.74	0.597	0.8%	9	1126
Vaginal adhesions	0.2%	1	430	0.9%	4	435	3.24	0.35 to 29.78	0.299	0.8%	3	367	1.1%	4	368	N/A	N/A	N/A	0.7%	8	1126
Haematoma	0.7%	3	430	1.4%	6	435	2.02	0.51 to 8.00	0.319	0.3%	1	367	1.1%	4	368	4.12	0.47 to 36.48	0.203	1.1%	12	1126
Skin tags	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.3%	1	368	N/A	N/A	N/A	0.3%	3	1126
Granulation tissue	0.2%	1	430	0.2%	1	435	0.99	0.06 to 15.75	0.993	0.3%	1	367	0.5%	2	368	1.96	0.18 to 21.53	0.582	0.0%	0	1126
Urinary tract symptoms	0.0%	0	430	0.5%	2	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0. 2%	2	1126
Death	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Any serious adverse effects (excluding mesh complications)	7.2%	31	430	7.8%	34	435	1.08	0.68 to 1.72	0.730	6.3%	23	367	9.8%	36	368	1.57	0.95 to 2.59	0.076	6.64%	74	1126
Serious adverse effects in second year																					
Number of women at 2 years	*N* = 430			*N* = 435						*N* = 367			*N* = 368						*N* = 1126		
Thrombosis	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Infection	0.2%	1	430	0.2%	1	435	0.98	0.46 to 2.08	0.957	0.0%	0	367	0.3%	1	368	N/A	N/A	N/A	0.4%	4	1126
Pain	0.5%	2	430	0.5%	2	435	1.014	0.14 to 7.11	0.991	0.3%	1	367	0.3%	1	368	1.00	0.06 to15.81	0.999	0.1%	1	1126
Urinary retention	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.1%	1	1126
Bowel obstruction	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126

continued

TABLE 22 Serious and related adverse effects within first and second years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									Cohort		
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Constipation	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Excess blood loss	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Vaginal adhesions	0.7%	3	430	0.0%	0	435	N/A	N/A	N/A	0.8%	3	367	0.8%	3	368	1.00	0.20 to 4.90	0.997	0.2%	2	1126
Haematoma	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.1%	1	1126
Skin tags	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Granulation tissue	0.2%	1	430	0.0%	0	435	N/A	N/A	N/A	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Urinary tract symptoms	0.0%	0	430	0.2%	1	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.1%	1	1126
Death	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Any serious adverse effects (excluding mesh complications)	1.4%	6	430	0.9%	4	435	0.66	0.19 to 2.30	0.510	1.1%	4	367	1.4%	5	368	1.25	0.34 to 4.60	0.740	0.6%	7	1126

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 23 Other related adverse effects within first and second years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Intraoperative complications																					
Number of women at 1 year	*N* = 430			*N* = 435						*N* = 367			*N* = 368						*N* = 1126		
Injury to organs	0.5%	2	430	0.0%	0	435	N/A	N/A	N/A	0.5%	2	367	0.3%	1	368	0.39	0.03 to 4.88	0.468	0.2%	2	1126
Excess blood loss	0.0%	0	430	0.2%	1	435	N/A	N/A	N/A	0.0%	0	367	0.3%	1	368	N/A	N/A	N/A	0.4%	5	1126
Blood transfusion	0.2%	1	430	0.0%	0	435	N/A	N/A	N/A	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Anaesthetic complications	0.5%	2	430	0.2%	1	435	0.49	0.04 to 5.43	0.564	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.4%	5	1126
Other adverse effects in first year																					
Thrombosis	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Infection	4.0%	17	430	1.8%	8	435	0.47	0.21 to 1.07	0.073	3.3%	12	367	2.2%	8	368	0.66	0.27 to 1.60	0.359	2.7%	30	1126
Pain	1.4%	6	430	1.4%	6	435	1.00	0.33 to 3.07	0.999	1.4%	5	367	0.8%	3	368	0.60	0.14 to 2.48	0.480	0.9%	10	1126
Urinary retention	1.2%	5	430	1.4%	6	435	1.18	0.37 to 3.84	0.778	2.2%	8	367	0.8%	3	368	0.38	0.10 to 1.41	0.146	1.1%	12	1126
Bowel obstruction	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Constipation	0.2%	1	430	0.2%	1	435	0.99	0.06 to 15.75	0.993	0.3%	1	367	0.8%	3	368	2.99	0.31 to 28.63	0.342	0.5%	6	1126
Excess blood loss	0.5%	2	430	0.2%	1	435	0.50	0.05 to 5.49	0.571	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.6%	7	1126

continued

TABLE 23 Other related adverse effects within first and second years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Vaginal adhesions	0.5%	2	430	0.5%	2	435	1.02	0.14 to 7.20	0.984	0.5%	2	367	0.3%	1	368	0.53	0.05 to 5.87	0.607	0.4%	5	1126
Haematoma	0.2%	1	430	0.2%	1	435	0.98	0.06 to 15.63	0.987	0.0%	0	367	0.5%	2	368	N/A	N/A	N/A	0.2%	2	1126
Skin tags	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Granulation tissue	0.5%	2	430	0.5%	2	435	0.99	0.14 to 6.99	0.991	0.5%	2	367	0.0%	0	368	N/A	N/A	N/A	0.3%	3	1126
Urinary tract symptoms	0.0%	0	430	0.2%	1	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.2%	2	1126
Any other adverse effects (excluding mesh complications)	8.1%	35	430	6.4%	28	435	0.79	0.49 to 1.28	0.340	7.64%	28	367	5.2%	19	368	0.68	0.39 to 1.19	0.175	6.3%	71	1126
Other adverse effects in second year																					
Number of women at 2 years	*N* = 430			*N* = 435						*N* = 367			*N* = 368						*N* = 1126		
Thrombosis	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Infection	0.5%	2	430	0.5%	2	435	0.99	0.14 to 7.01	0.994	0.3%	1	367	1.1%	4	368	3.95	0.44 to 35.17	0.218	0.3%	3	1126
Pain	1.2%	5	430	0.7%	3	435	0.61	0.15 to 2.54	0.449	0.5%	2	367	0.8%	3	368	1.49	0.25 to 8.83	0.661	0.2%	2	1126
Urinary retention	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Bowel obstruction	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0		0.0%	0		N/A	N/A	N/A	0.0%	0	1126
Constipation	0.7%	3	430	0.0%	0	435	N/A	N/A	N/A	0.5%	2	367	0.0%	0	368	N/A	N/A	N/A	0.1%	1	1126
Excess blood loss	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.1%	1	1126

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft												
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Vaginal adhesions	0.9%	4	430	0.2%	1	435	0.24	0.03 to 2.17	0.206	1.4%	5	367	0.3%	1	368	0.21	0.02 to 1.77	0.15	0.0%	0	1126
Haematoma	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Skin tags	0.0%	0	430	0.0%	0	435	N/A	N/A	N/A	0.0%	0	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Granulation tissue	0.1%	1	430	0.2%	1	435	0.99	0.06 to 15.66	0.992	0.3%	1	367	0.0%	0	368	N/A	N/A	N/A	0.0%	0	1126
Urinary tract symptoms	0.0%	0	430	0.2%	1	435	N/A	N/A	N/A	0.0%	0	367	0.3%	1	368	N/A	N/A	N/A	0.0%	0	1126
Any other adverse effects (excluding mesh complications)	3.0%	13	430	1.6%	7	435	0.53	0.21 to 1.32	0.172	3.0%	11	367	2.4%	9	368	0.80	0.34 to 1.90	0.613	0.5%	6	1126

N/A, not applicable.
Dichotomous variables are presented as '% *n* *N*'.

TABLE 24 Prolapse symptoms at 6 months, 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft										CC1		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Six-month outcomes																						
Number of women at 6 months	*N* = 398			*N* = 381						*N* = 338			*N* = 335						*N* = 966		
POP-SS at 6 months	4.7	(5.4)	398	5.3	(5.1)	380	0.57	–0.12 to 1.26	0.104	5.0	(5.5)	338	4.9	(5.5)	335	–0.44	–1.23 to 0.35	0.275	4.8	(5.1)	959
Symptomatic	78.9%	314	398	85.5%	325	380	1.07	1.00 to 1.14	0.038	81.1%	274	338	80.9%	271	335	1.00	0.93 to 1.08	0.956	81.0%	777	959
Prolapse-related QoL score	2.0	(2.8)	390	2.2	(2.7)	374	0.22	–0.16 to 0.60	0.262	2.0	(2.9)	332	2.0	(2.7)	330	–0.17	–0.58 to 0.25	0.428	2.1	(2.8)	946
1-year outcomes																						
Number of women at 1 year	*N* = 395			*N* = 389						*N* = 342			*N* = 337						*N* = 972		
POP-SS at 1 year	5.4	(5.5)	395	5.5	(5.1)	389	0.00	–0.70 to 0.71	0.989	5.5	(5.6)	342	5.6	(5.6)	337	–0.15	–0.93 to 0.63	0.706	5.2	(5.3)	963
Symptomatic	83.0%	328	395	84.6%	329	389	1.01	0.95 to 1.08	0.641	82.7%	283	342	81.9%	276	337	0.99	0.93 to 1.06	0.848	83.5%	804	963
Prolapse-related QoL score	2.0	(2.7)	389	2.2	(2.7)	380	0.13	–0.25 to 0.51	0.500	2.2	(2.8)	335	2.4	(2.9)	330	0.13	–0.30 to 0.56	0.544	2.3	(2.8)	942

Symptom	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft										CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
2-year outcomes																						
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300							*N* = 848		
POP-SS at 2 years	4.9	(5.1)	347	5.3	(5.1)	342	0.32	–0.39 to 1.03	0.372	4.9	(5.1)	298	5.5	(5.7)	299	0.32	–0.48 to 1.12	0.430	5.3	(5.1)	833
Other measures of prolapse symptoms																						
Symptomatic	81.6%	283	347	85.1%	291	342	1.04	0.97 to 1.11	0.296	81.2%	242	298	81.9%	245	299	0.99	0.92 to 1.07	0.846	86.2%	718	833
Prolapse-related QoL score	1.9	(2.5)	335	2.2	(2.6)	329	0.15	–0.23 to 0.54	0.435	2.0	(2.5)	290	2.2	(2.8)	291	0.10	–0.33 to 0.52	0.662	2.2	(2.7)	811

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome; *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

TABLE 25 Individual prolapse symptoms at 6 months, 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Six-month outcomes																					
Number of women at 6 months	*N* = 398			*N* = 381						*N* = 338			*N* = 335						*N* = 966		
Individual prolapse symptoms																					
SCD any	30.9%	123	398	32.9%	125	380	1.09	0.90 to 1.34	0.377	29.9%	101	338	33.7%	113	335	1.11	0.88 to 1.39	0.376	30.6%	293	959
SCD freq.	7.8%	31	398	9.7%	37	380	1.21	0.77 to 1.90	0.403	9.2%	31	338	11.0%	37	335	1.08	0.68 to 1.71	0.745	8.6%	82	959
Pain any	25.4%	101	398	27.4%	104	380	1.08	0.86 to 1.36	0.509	25.1%	85	338	24.2%	81	335	0.90	0.69 to 1.18	0.452	25.1%	241	959
Pain freq.	4.8%	19	398	6.1%	23	380	1.22	0.69 to 2.15	0.503	5.9%	20	338	5.4%	18	335	0.78	0.41 to 1.50	0.465	4.8%	46	959
Abdo. any	27.4%	109	398	35.3%	134	380	1.22	0.99 to 1.50	0.058	27.5%	93	338	34.9%	117	335	1.13	0.90 to 1.41	0.300	30.9%	296	959
Abdo. freq.	3.8%	15	398	5.0%	19	380	1.26	0.66 to 2.43	0.484	4.1%	14	338	3.9%	13	335	0.56	0.24 to 1.29	0.175	4.3%	41	959
Back any	33.4%	133	398	38.9%	148	380	1.17	0.98 to 1.40	0.082	34.0%	115	338	38.8%	130	335	1.15	0.95 to 1.39	0.161	34.1%	327	959
Back freq.	7.5%	30	398	7.4%	28	380	0.94	0.59 to 1.51	0.793	9.5%	32	338	8.7%	29	335	0.75	0.46 to 1.23	0.261	7.2%	69	959
Strain blad. any	36.2%	144	398	38.2%	145	380	1.08	0.91 to 1.29	0.367	36.4%	123	338	37.0%	124	335	0.99	0.81 to 1.21	0.927	37.6%	361	959
Strain blad. freq.	10.1%	40	398	8.2%	31	380	0.83	0.53 to 1.28	0.391	11.2%	38	338	8.1%	27	335	0.71	0.44 to 1.15	0.164	6.8%	65	959
Blad. not empty any	52.0%	207	398	57.6%	219	380	1.11	0.98 to 1.25	0.100	53.3%	180	338	50.1%	168	335	0.88	0.76 to 1.01	0.073	55.4%	531	959
Blad. not empty freq.	13.3%	53	398	13.9%	53	380	1.10	0.78 to 1.55	0.585	13.3%	45	338	13.1%	44	335	0.88	0.60 to 1.30	0.531	10.9%	105	959

Symptom	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Bowel not empty any	60.1%	239	398	62.1%	236	380	1.05	0.94 to 1.16	0.382	61.8%	209	338	55.2%	185	335	0.90	0.80 to 1.02	0.101	58.7%	563	959
Bowel not empty freq.	12.1%	48	398	13.2%	50	380	1.17	0.81 to 1.68	0.406	16.0%	54	338	11.0%	37	335	0.71	0.48 to 1.03	0.070	10.9%	105	959
1-year outcomes																					
Number of women at 1 year	*N* = 395			*N* = 389						*N* = 342			*N* = 337						*N* = 972		
Individual prolapse symptoms																					
SCD any	36.2%	143	395	35.5%	138	389	0.98	0.82 to 1.18	0.849	34.2%	117	342	41.5%	140	337	1.18	0.97 to 1.43	0.103	34.8%	335	963
SCD freq.	9.1%	36	395	9.8%	38	389	1.08	0.70 to 1.66	0.740	10.8%	37	342	11.6%	39	337	1.00	0.65 to 1.54	0.999	7.9%	76	963
Pain any	25.6%	101	395	30.6%	119	389	1.20	0.96 to 1.51	0.103	25.1%	86	342	30.6%	103	337	1.21	0.94 to 1.54	0.132	28.0%	270	963
Pain freq.	4.3%	17	395	4.6%	18	389	1.01	0.53 to 1.92	0.970	5.0%	17	342	5.3%	18	337	0.90	0.47 to 1.73	0.751	5.3%	51	963
Abdo. any	31.6%	125	395	35.5%	138	389	1.07	0.88 to 1.30	0.506	32.2%	110	342	33.2%	112	337	0.99	0.79 to 1.23	0.909	31.7%	305	963
Abdo. freq.	5.6%	22	395	4.6%	18	389	0.85	0.46 to 1.59	0.608	5.8%	20	342	6.2%	21	337	0.97	0.52 to 1.79	0.917	4.4%	42	963
Back any	36.2%	143	395	39.3%	153	389	1.07	0.90 to 1.28	0.431	37.4%	128	342	38.0%	128	337	1.06	0.88 to 1.28	0.542	37.3%	359	963
Back freq.	7.8%	31	395	8.2%	32	389	1.05	0.66 to 1.65	0.848	7.9%	27	342	9.8%	33	337	1.19	0.74 to 1.93	0.469	7.9%	76	963

continued

TABLE 25 Individual prolapse symptoms at 6 months, 1 year and 2 years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Strain blad. any	44.1%	174	395	41.6%	162	389	0.93	0.80 to 1.08	0.350	42.1%	144	342	40.4%	136	337	0.88	0.74 to 1.05	0.156	39.7%	382	963
Strain blad. freq.	10.9%	43	395	7.2%	28	389	0.63	0.41 to 0.99	0.045	11.7%	40	342	10.4%	35	337	0.81	0.53 to 1.25	0.340	9.2%	89	963
Blad. not empty any	56.7%	224	395	59.9%	233	389	1.03	0.92 to 1.15	0.585	55.8%	191	342	56.7%	191	337	0.95	0.84 to 1.08	0.471	57.7%	556	963
Blad. not empty freq.	13.9%	55	395	11.6%	45	389	0.83	0.57 to 1.19	0.307	14.6%	50	342	12.8%	43	337	0.84	0.58 to 1.21	0.337	11.8%	114	963
Bowel not empty any	63.8%	252	395	66.6%	259	389	1.01	0.92 to 1.11	0.771	62.9%	215	342	65.3%	220	337	1.08	0.97 to 1.20	0.153	61.8%	595	963
Bowel not empty freq.	15.9%	63	395	12.6%	49	389	0.83	0.59 to 1.15	0.263	16.7%	57	342	12.8%	43	337	0.77	0.54 to 1.09	0.137	11.8%	114	963
Actions necessitated by prolapse symptoms																					
Fingers to ease discomfort	1.1%	4	352	1.2%	4	347	1.19	0.30 to 4.64	0.803	1.3%	4	308	1.9%	6	309	1.42	0.32 to 6.31	0.643	1.1%	9	854
Extra hygiene measures	5.7%	20	349	6.6%	23	349	1.16	0.65 to 2.05	0.620	7.5%	23	308	5.3%	16	304	0.57	0.29 to 1.13	0.106	4.9%	42	859
Fingers to help empty bladder	0.3%	1	364	0.8%	3	353	3.16	0.33 to 30.64	0.321	0.0%	0	313	0.6%	2	311	N/A	N/A	N/A	0.6%	5	875
Fingers to help empty bowel	2.0%	7	358	1.7%	6	349	0.86	0.30 to 2.47	0.776	1.9%	6	311	1.9%	6	311	0.98	0.32 to 2.99	0.972	2.7%	24	873
Digital evacuation of bowel	3.0%	11	366	1.7%	6	357	0.54	0.21 to 1.41	0.207	3.8%	12	315	1.9%	6	314	0.40	0.15 to 1.09	0.072	3.3%	29	881

Symptom	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Individual prolapse symptoms																					
SCD any	30.5%	106	347	33.9%	116	342	1.06	0.85 to 1.32	0.592	30.5%	91	298	40.1%	120	299	1.26	1.01 to 1.58	0.042	34.9%	291	833
SCD freq.	6.3%	22	347	7.9%	27	342	1.27	0.74 to 2.16	0.383	5.7%	17	298	11.4%	34	299	1.80	1.03 to 3.15	0.041	8.0%	67	833
Pain any	21.3%	74	347	28.7%	98	342	1.32	1.01 to 1.71	0.040	21.8%	65	298	27.1%	81	299	1.23	0.93 to 1.64	0.152	25.3%	211	833
Pain freq.	2.9%	10	347	2.6%	9	342	0.79	0.32 to 1.95	0.610	2.3%	7	298	3.3%	10	299	1.18	0.45 to 3.10	0.735	4.8%	40	833
Abdo. any	30.8%	107	347	32.5%	111	342	0.99	0.80 to 1.23	0.943	30.9%	92	298	32.1%	96	299	1.01	0.80 to 1.28	0.921	33.0%	275	833
Abdo. freq.	4.3%	15	347	3.5%	12	342	0.78	0.37 to 1.61	0.495	4.0%	12	298	5.4%	16	299	1.03	0.49 to 2.16	0.939	3.5%	29	833
Back any	37.5%	130	347	42.7%	146	342	1.08	0.91 to 1.29	0.377	37.6%	112	298	34.1%	102	299	0.92	0.75 to 1.12	0.392	39.0%	325	833
Back freq.	6.6%	23	347	6.4%	22	342	0.86	0.50 to 1.49	0.601	6.4%	19	298	6.7%	20	299	0.91	0.50 to 1.65	0.754	7.6%	63	833
Strain blad. any	39.2%	136	347	43.3%	148	342	1.05	0.89 to 1.24	0.581	38.6%	115	298	45.5%	136	299	1.06	0.88 to 1.27	0.520	41.9%	349	833
Strain blad. freq.	7.5%	26	347	6.7%	23	342	0.80	0.46 to 1.38	0.421	9.4%	28	298	10.7%	32	299	0.99	0.61 to 1.60	0.962	8.6%	72	833
Blad. not empty any	54.8%	190	347	62.9%	215	342	1.14	1.01 to 1.28	0.037	54.4%	162	298	58.2%	174	299	0.99	0.86 to 1.13	0.838	62.3%	519	833
Blad. not empty freq.	11.0%	38	347	10.5%	36	342	0.86	0.55 to 1.34	0.497	12.8%	38	298	14.4%	43	299	0.95	0.64 to 1.40	0.780	10.8%	90	833

continued

TABLE 25 Individual prolapse symptoms at 6 months, 1 year and 2 years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft												
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Bowel not empty any	65.1%	226	347	67.3%	230	342	1.00	0.90 to 1.10	0.936	66.4%	198	298	65.2%	195	299	0.97	0.88 to 1.09	0.642	66.7%	556	833
Bowel not empty freq.	13.3%	46	347	13.7%	47	342	1.06	0.74 to 1.54	0.745	13.8%	41	298	13.4%	40	299	0.99	0.67 to 1.46	0.957	10.8%	90	833
Actions necessitated by prolapse symptoms																					
Fingers to ease discomfort	1.7%	6	343	0.9%	3	331	0.45	0.11 to 1.87	0.269	1.4%	4	295	2.1%	6	288	1.54	0.42 to 5.65	0.514	1.1%	9	825
Extra hygiene measures	5.6%	19	341	5.2%	17	330	0.93	0.48 to 1.77	0.815	5.1%	15	293	6.6%	19	287	1.21	0.61 to 2.41	0.579	5.0%	41	823
Fingers to help empty bladder	0.6%	2	347	0.6%	2	338	2.02	0.18 to 22.20	0.566	0.7%	2	298	1.3%	4	298	2.07	0.38 to 11.31	0.400	0.5%	4	835
Fingers to help empty bowel	2.7%	9	336	2.4%	8	335	0.92	0.38 to 2.24	0.859	2.8%	8	289	0.3%	1	293	0.12	0.02 to 0.97	0.046	3.5%	29	830
Digital evacuation of bowel	2.6%	9	342	0.6%	2	337	0.29	0.06 to 1.37	0.118	4.7%	14	295	1.4%	4	296	0.33	0.11 to 0.97	0.044	3.5%	29	838

N/A, not applicable.
Dichotomous variables are presented as '% *n N*'.

Individual prolapse symptoms

Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time.; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely?' (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad.* any: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.

Actions necessitated by prolapse symptoms

Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

- the proportion of women who had at least one prolapse symptom ('symptomatic' defined as POP-SS of > 0)
- the prolapse-related QoL score measured as the interference of prolapse symptoms with everyday life, *and*
- the need to undertake extra hygiene measures or manoeuvres to ease discomfort or to assist pelvic floor functions, such as emptying the bladder or bowel.

All of these measures demonstrated significant improvements from before surgery, but no difference between the randomised groups at any time point in either trial (see *Tables 24* and *25*).

The improvement at 1 year was maintained at 2 years, with respect to all of the prolapse outcomes and QoL outcomes measured. However, there were still no statistically significant differences between the randomised groups in either trial. The data from the cohort women were similar (see *Tables 24* and *25*).

EuroQol-5 Dimensions (3-level version)

There were no statistically significant differences between the randomised groups in the generic EQ-5D-3L QoL scores at 6 months, 1 year or 2 years in either trial 1 or trial 2 (*Table 26*). However, the score improved from baseline levels in all the groups of women. The data from the cohort women were similar. This outcome is further explored in the section on economic outcomes in *Chapter 5*.

Specifically the EQ-5D-3L scores at 1 year were compared (see *Table 26*).

1. In trial 1, the MD in the EQ-5D-3L scores for standard repair (0.830) compared with synthetic mesh inlay (0.834), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), was MD 0.01, 95% CI –0.02 to 0.04.
2. In trial 2, the MD for standard repair (0.81) compared with biological graft (0.82), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), was MD 0.02, 95% CI –0.01 to 0.06.

The EQ-5D-3L scores at 2 years were virtually unchanged (see *Table 26*):

1. In trial 1, the MD in the EQ-5D-3L scores for standard repair (0.81) compared with synthetic mesh inlay (0.83), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), was MD 0.02, 95% CI –0.02 to 0.06.
2. In trial 2, the MD for standard repair (0.81) compared with biological graft (0.82), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), was MD 0.03, 95% CI –0.01 to 0.07.

Urinary symptoms

Detailed information on urinary symptoms was obtained at baseline, 1 year and 2 years. The proportion of women who had concomitant continence surgery ranged from 9.7% to 12.1% (see *Table 19*). There was an overall decrease of 10% in the proportion of women who had any UI (from around 77% to around 65%) and the proportion with severe UI more than halved (from around 20% to around 7%) at 1 year (see *Tables 16* and *27*).

The findings were virtually unchanged by 2 years: there did not appear to be any further recovery or deterioration in urinary symptoms over that time span. However, there was no difference between the randomised groups with respect to any of the urinary outcomes measured at 1 or 2 years in either trial (*Table 27*). The data from the cohort women were similar.

TABLE 26 EuroQol-5 Dimensions (3-level version) at 6 months, 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh								Trial 2: standard repair vs. biological graft									
EQ-5D-3L	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
At 6 months																		
Number of women	*N* = 398			*N* = 381						*N* = 338			*N* = 335					
Score	0.82	(0.26)	383	0.83	(0.22)	372	0.01	–0.02 to 0.04	0.400	0.82	(0.27)	326	0.82	(0.25)	318	0.01	–0.02 to 0.05	0.499
At 1 year																		
Number of women	*N* = 395			*N* = 389						*N* = 342			*N* = 337					
Score	0.83	(0.25)	385	0.83	(0.22)	384	0.01	–0.02 to 0.04	0.651	0.81	(0.27)	335	0.82	(0.25)	333	0.02	–0.01 to 0.06	0.205
At 2 years																		
Number of women	*N* = 348			*N* = 343						*N* = 299			*N* = 300					
Score	0.81	(0.28)	340	0.83	(0.22)	334	0.02	–0.02 to 0.06	0.257	0.81	(0.28)	291	0.82	(0.27)	294	0.03	–0.01 to 0.07	0.170

CC1		
N = 966		
0.83	(0.24)	935
N = 972		
0.83	(0.25)	949
N = 848		
0.83	(0.24)	821

Continuous variables are presented as 'mean (SD) *N*'.

TABLE 27 Urinary symptoms at 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
1-year outcomes																					
Number of women at 1 year	*N* = 368			*N* = 362						*N* = 319			*N* = 316						*N* = 893		
Any incontinence	63.9%	235	368	64.9%	235	362	1.00	0.91 to 1.10	0.977	64.9%	207	319	64.2%	203	316	0.98	0.89 to 1.08	0.673	65.6%	586	893
ICIQ-UI-SF score	4.1	(4.3)	361	4.4	(4.7)	354	0.29	–0.30 to 0.88	0.333	4.4	(4.6)	315	4.1	(4.3)	313	–0.44	–1.04 to 0.15	0.144	4.4	(4.5)	876
Severe incontinence	5.8%	21	361	8.2%	29	354	1.34	0.79 to 2.26	0.274	8.3%	26	315	5.4%	17	313	0.61	0.33 to 1.12	0.110	7.0%	61	876
UI QoL score	1.6	(2.3)	345	1.8	(2.6)	344	0.21	–0.13 to 0.55	0.229	1.8	(2.5)	301	1.6	(2.4)	302	–0.16	–0.52 to 0.19	0.361	1.7	(2.5)	859
Stress UI	8.4%	24	286	8.1%	24	296	1.11	0.64 to 1.92	0.715	10.8%	27	251	10.6%	27	255	1.26	0.78 to 2.05	0.340	11.0%	80	728
Urgency UI	3.3%	12	366	5.3%	19	361	1.59	0.79 to 3.22	0.195	4.1%	13	318	2.2%	7	314	0.47	0.19 to 1.14	0.093	4.5%	40	891
Overactive bladder	1.4%	5	363	2.3%	8	355	1.69	0.56 to 5.08	0.352	1.9%	6	315	0.3%	1	313	0.16	0.02 to 1.31	0.087	1.8%	16	883
ICIQ-FLUTS filling score	3.6	(2.4)	363	3.8	(2.4)	355	0.10	–0.19 to 0.39	0.500	3.7	(2.6)	315	3.7	(2.4)	311	–0.19	–0.50 to 0.12	0.234	3.7	(2.4)	879
ICIQ-FLUTS voiding score	1.8	(2.1)	363	2.0	(2.0)	359	0.22	–0.06 to 0.50	0.120	1.9	(2.1)	317	1.9	(2.0)	313	0.02	–0.27 to 0.31	0.895	1.8	(2.1)	887
ICIQ-FLUTS incontinence	4.2	(3.3)	279	4.3	(3.5)	288	0.25	–0.27 to 0.78	0.345	4.6	(3.6)	247	4.2	(3.5)	250	–0.38	–0.94 to 0.18	0.182	4.5	(3.7)	713

continued

TABLE 27 Urinary symptoms at 1 year and 2 years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Any incontinence	65.5%	228	348	66.9%	228	341	1.00	0.91 to 1.11	0.947	65.6%	196	299	62.7%	188	300	0.94	0.85 to 1.03	0.188	66.9%	567	848
ICIQ-UI-SF score	4.2	(4.4)	343	4.4	(4.3)	334	0.00	–0.59 to 0.59	0.998	4.3	(4.5)	294	4.1	(4.4)	297	–0.49	–1.11 to 0.13	0.121	4.4	(4.7)	829
Severe incontinence	5.5%	19	343	6.3%	21	334	1.01	0.51 to 1.99	0.974	7.1%	21	294	6.7%	20	297	0.80	0.44 to 1.46	0.468	8.6%	71	829
UI QoL score	1.6	(2.4)	337	1.8	(2.4)	329	–0.02	–0.36 to 0.33	0.930	1.7	(2.4)	289	1.7	(2.5)	290	–0.12	–0.49 to 0.24	0.513	1.8	(2.6)	826
Stress UI	8.0%	24	301	8.3%	24	290	1.05	0.59 to 1.86	0.867	9.2%	24	262	8.2%	21	256	0.91	0.53 to 1.56	0.735	9.8%	72	733
Urgency UI	3.4%	12	348	5.3%	18	339	1.74	0.74 to 4.07	0.205	3.0%	9	299	4.3%	13	299	1.27	0.55 to 2.89	0.576	5.6%	47	840
Overactive bladder	1.4%	5	346	3.0%	10	338	1.97	0.69 to 5.68	0.207	1.7%	5	297	1.7%	5	296	0.56	0.16 to 1.96	0.367	2.0%	17	835
ICIQ-FLUTS filling score	3.8	(2.6)	343	4.0	(2.5)	335	0.09	–0.26 to 0.44	0.631	3.9	(2.6)	293	3.8	(2.5)	296	–0.32	–0.65 to 0.02	0.062	3.8	(2.4)	831
ICIQ-FLUTS voiding score	1.8	(2.2)	343	2.0	(2.1)	338	0.10	–0.21 to 0.41	0.531	1.9	(2.2)	296	2.0	(2.3)	298	–0.03	–0.35 to 0.30	0.864	1.9	(2.1)	839
ICIQ-FLUTS incontinence	4.0	(3.5)	294	4.3	(3.3)	281	0.14	–0.39 to 0.67	0.602	4.1	(3.6)	255	4.1	(3.7)	252	–0.40	–0.98 to 0.18	0.175	4.2	(3.7)	715

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

Bowel symptoms

Detailed information on bowel symptoms was obtained at baseline, 1 year and 2 years. Bowel frequency and urgency were largely unchanged after prolapse surgery (*Table 28*). However, fewer women had constipation or FI; this improvement was reflected in the bowel symptoms QoL score, which was around half of the baseline level at both 1 year and 2 years after surgery (see *Tables 17* and *28*). Nevertheless, there was no difference between the randomised groups with respect to any of the bowel outcomes measured at 1 year or 2 years in either trial (see *Table 28*). The data from the cohort women were similar.

Vaginal and sexual symptoms

Detailed information on vaginal and sexual symptoms was obtained at baseline, 1 year and 2 years (see *Tables 18* and *29*). Both the mean vaginal symptom score and the QoL decreased (improved) after prolapse surgery (*Table 29*).

More women were sexually active after surgery (increased from < 40% before to around 50% after) and fewer cited prolapse symptoms as a reason for not having a sex life (reduced from > 40% to < 15%). This was reflected in a halving of the ICI Sexual Matters score, and a greater reduction (improvement) in the sex life QoL score. The rates for dyspareunia were low both before (around 9%) and after surgery (around 5%; see *Tables 18* and *29*). However, there was no difference between the randomised groups with respect to any of the vaginal or sexual symptom outcomes measured. The improvements in these outcomes were maintained at 2 years, but still with no differences between the randomised groups in either trial (see *Table 29*). The data from the cohort women were similar.

Postoperative prolapse measurements in randomised women

A 1-year clinic review was offered to all randomised women and 88% attended. Objective measurement showed improvement in each of the three prolapse compartments (*Table 30*). The proportion of women with the leading prolapse edge beyond the hymen (> 0 cm) reduced substantially. Nevertheless, just under 20% of women still had residual prolapse.

Specifically, the RR for the proportion of women with residual prolapse beyond the hymen at 1 year (see *Table 30*) was:

1. In trial 1, in the standard repair group (13.9%) compared with synthetic mesh inlay (16.1%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), RR 1.12, 95% CI 0.79 to 1.60.
2. In trial 2, in the standard repair group (15.5%) compared with biological graft (18.1%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), RR 1.14, 95% CI 0.80 to 1.62.

Thus, the finding that more women appeared to have residual prolapse after mesh or graft repair than after standard repair was not statistically significant, and the difference was so small that it is not likely to be clinically significant.

Readmissions and further treatment required for failure and adverse effects at 6 months, 1 year and 2 years

When women reported that, at 6 months or later, they had been readmitted to hospital, we verified the information by enquiry from centre staff when necessary and post-coded the corrected information.

TABLE 28 Bowel symptoms at 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft												
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
1-year outcomes																						
Number of women at 1 year	*N* = 368			*N* = 362						*N* = 319			*N* = 316						*N* = 893		
Bowel frequency																						
> 3 daily	4.4%	16	365	2.5%	9	359	0.85	0.62 to 1.14	0.277	4.5%	14	314	2.9%	9	312	0.86	0.62 to 1.19	0.363	3.6%	32	883
1–3 times daily	27.9%	102	365	30.1%	108	359				33.4%	105	314	32.1%	100	312				27.4%	242	883
Once daily	46.3%	169	365	46.8%	168	359				41.4%	130	314	43.9%	137	312				49.5%	437	883
Every 2–3 days	18.4%	67	365	17.8%	64	359				18.2%	57	314	19.2%	60	312				17.9%	158	883
Weekly or less	3.0%	11	365	2.8%	10	359				2.5%	8	314	1.9%	6	312				1.6%	14	883
Constipation	14.0%	51	365	12.6%	45	357	1.04	0.73 to 1.48	0.811	14.7%	46	313	13.5%	42	310	0.96	0.66 to 1.40	0.835	14.1%	123	871
Bowel urgency	8.2%	30	364	4.7%	17	359	0.62	0.36 to 1.08	0.091	7.6%	24	314	5.1%	16	314	0.62	0.34 to 1.13	0.118	6.7%	59	887
FI (any)	27.9%	102	365	25.4%	91	358	0.92	0.74 to 1.13	0.411	26.6%	84	316	24.5%	77	314	0.92	0.72 to 1.17	0.495	27.1%	240	885
Passive FI	74.5%	76	102	84.6%	77	91				76.2%	64	84	85.7%	66	77				80.4%	193	240
Active FI	25.5%	26	102	15.4%	14	91				23.8%	20	84	14.3%	11	77				19.6%	47	240
Severe FI	6.6%	24	365	7.3%	26	358	1.18	0.70 to 1.99	0.537	5.7%	18	316	8.9%	28	314	1.33	0.75 to 2.35	0.334	6.4%	57	885
Bowel symptoms QoL	1.8	(2.4)	359	1.7	(2.3)	348	0.03	–0.29 to 0.35	0.859	1.9	(2.4)	313	1.7	(2.4)	310	–0.13	–0.48 to 0.23	0.483	1.9	(2.5)	869

Symptom	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Bowel frequency																					
> 3 daily	5.0%	17	343	4.7%	16	338	1.03	0.76 to 1.40	0.848	6.1%	18	296	3.4%	10	298	1.30	0.93 to 1.81	0.130	3.1%	26	843
1–3 times daily	27.1%	93	343	28.4%	96	338				33.1%	98	296	30.2%	90	298				31.0%	261	843
Once daily	48.7%	167	343	48.8%	165	338				40.9%	121	296	47.0%	140	298				48.5%	409	843
Every 2–3 days	15.7%	54	343	15.4%	52	338				16.9%	50	296	17.4%	52	298				15.9%	134	843
Weekly or less	3.5%	12	343	2.7%	9	338				3.0%	9	296	2.0%	6	298				1.5%	13	843
Constipation	12.7%	43	338	11.6%	39	335	0.95	0.65 to 1.41	0.814	13.7%	40	292	12.2%	36	296	0.89	0.60 to 1.32	0.568	12.6%	104	825
Bowel urgency	8.2%	28	343	3.8%	13	338	0.50	0.26 to 0.97	0.040	7.8%	23	294	6.1%	18	297	0.70	0.38 to 1.29	0.252	5.8%	49	839
FI (any)	25.9%	89	343	27.2%	92	338	1.13	0.92 to 1.41	0.249	27.5%	81	295	25.8%	77	298	0.95	0.75 to 1.21	0.692	24.6%	206	837
Passive FI	74.2%	66	89	87.0%	80	92				76.5%	62	81	80.5%	62	77				80.1%	165	206
Active FI	25.8%	23	89	13.0%	12	92				23.5%	19	81	19.5%	15	77				19.9%	41	206
Severe FI	7.9%	27	343	5.0%	17	338	0.71	0.40 to 1.26	0.245	6.8%	20	295	10.1%	30	298	1.09	0.64 to 1.86	0.747	7.3%	61	837
Bowel symptoms QoL	1.8	(2.6)	333	1.7	(2.3)	337	–0.05	–0.40 to 0.30	0.767	1.9	(2.5)	288	1.7	(2.4)	294	–0.09	–0.45 to 0.27	0.623	1.9	(2.6)	823

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: Any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 29 Vaginal and sexual symptoms at 1 year and 2 years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft										CC1		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
1-year outcomes																					
Number of women at 1 year	*N* = 368			*N* = 362						*N* = 319			*N* = 316						*N* = 893		
Vaginal																					
ICIQ-VS	7.2	(7.2)	338	7.5	(8.1)	327	0.52	–0.64 to 1.68	0.381	7.1	(6.9)	294	9.0	(9.1)	294	1.31	0.04 to 2.59	0.044	7.9	(8.5)	804
Vaginal symptoms QoL	1.4	(2.3)	346	1.6	(2.4)	343	0.14	–0.20 to 0.48	0.432	1.5	(2.3)	301	1.8	(2.6)	306	0.33	–0.06 to 0.72	0.098	1.8	(2.6)	847
Vagina too tight	3.2%	11	349	2.0%	7	348	0.55	0.20 to 1.45	0.226	3.0%	9	305	3.0%	9	305	1.00	0.42 to 2.41	0.992	2.8%	24	850
Sexual																					
Sex life at present	48.6%	175	360	46.9%	169	360				44.1%	138	313	48.7%	152	312				48.5%	426	878
Reason for no sex life																					
No partner	37.3%	69	185	38.2%	73	191				34.3%	60	175	35.6%	57	160				38.1%	172	452
Vaginal symptoms	7.0%	13	185	5.2%	10	191				9.1%	16	175	8.1%	13	160				5.8%	26	452
Prolapse symptoms	11.4%	21	185	11.0%	21	191				13.7%	24	175	15.0%	24	160				9.5%	43	452
Other reason	38.4%	71	185	38.7%	74	191				37.1%	65	175	32.5%	52	160				39.4%	178	452
Reason not given	5.9%	11	185	6.8%	13	191				5.7%	10	175	8.8%	14	160				7.3%	33	452

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Dyspareunia	4.3%	8	186	5.2%	9	173	1.73	0.52 to 5.78	0.373	6.0%	9	149	4.8%	8	165	1.17	0.43 to 3.23	0.758	5.4%	24	445
ICI Sexual Matters score	11.3	(12.9)	180	11.2	(13.1)	173	–0.40	–3.27 to 2.46	0.781	12.2	(13.3)	144	10.9	(13.1)	163	–2.46	–5.60 to 0.69	0.126	12.0	(13.9)	439
Sex life QoL score	2.7	(3.2)	184	3.0	(3.4)	184	0.47	–0.23 to 1.16	0.189	3.0	(3.4)	150	2.6	(3.4)	164	–0.57	–1.30 to 0.17	0.128	2.8	(3.2)	448
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Vaginal																					
ICIQ-VS	7.0	(7.3)	313	7.3	(7.8)	311	–0.18	–1.34 to 0.98	0.755	6.8	(6.8)	271	8.1	(8.8)	278	0.36	–0.95 to 1.67	0.585	7.4	(8.1)	772
Vaginal symptoms QoL	1.5	(2.3)	331	1.7	(2.4)	332	0.12	–0.23 to 0.47	0.497	1.3	(2.1)	283	1.6	(2.4)	283	0.15	–0.21 to 0.51	0.422	1.6	(2.5)	805
Vagina too tight	3.3%	11	329	0.9%	3	329	0.16	0.04 to 0.74	0.018	2.8%	8	283	2.4%	7	288	0.84	0.31 to 2.25	0.726	2.8%	23	811

continued

TABLE 29 Vaginal and sexual symptoms at 1 year and 2 years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Sexual																					
Sex life at present	47.3%	159	336	42.2%	139	329				42.1%	120	285	50.3%	147	292				47.5%	391	824
Reason for no sex life																					
No partner	29.9%	53	177	34.2%	65	190				30.3%	50	165	34.5%	50	145				33.3%	144	433
Vaginal symptoms	6.8%	12	177	2.6%	5	190				8.5%	14	165	6.2%	9	145				6.5%	28	433
Prolapse symptoms	9.0%	16	177	8.4%	16	190				9.7%	16	165	9.7%	14	145				7.4%	32	433
Other reason	40.1%	71	177	39.5%	75	190				38.8%	64	165	29.7%	43	145				35.6%	154	433
Reason not given	14.1%	25	177	15.3%	29	190				12.7%	21	165	20.0%	29	145				17.3%	75	433
Dyspareunia	5.4%	9	166	2.8%	4	145	0.49	0.15 to 1.55	0.223	4.0%	5	125	3.9%	6	154	0.93	0.29 to 2.99	0.903	5.0%	20	400
ICI Sexual Matters score	10.6	(13.0)	166	10.3	(12.5)	145	–0.15	–3.17 to 2.88	0.923	10.1	(12.8)	125	10.0	(12.3)	152	–0.62	–3.85 to 2.61	0.706	12.2	(14.1)	399
Sex life QoL score	2.3	(3.0)	164	2.5	(3.1)	151	0.13	–0.59 to 0.84	0.728	2.1	(2.8)	126	2.3	(3.0)	157	0.13	–0.59 to 0.85	0.728	2.7	(3.2)	402

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

TABLE 30 Objective measures of prolapse at 1-year clinic review: Primary trial

POP-Q measurement/stage	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
Number of women	*N* = 381			*N* = 374						*N* = 319			*N* = 319					
POP-Q measurement (cm)																		
Ba (posterior edge)	–1.3	(1.6)	323	–1.3	(1.6)	327	0.06	–0.17 to 0.29	0.622	–1.3	(1.7)	299	–1.2	(1.7)	293	0.12	–0.1 to 0.4	0.344
C (cervix/vault)	–6.0	(2.1)	318	–6.0	(2.3)	321	–0.03	–0.36 to 0.31	0.875	–5.8	(1.9)	292	–5.7	(2.1)	292	0.15	–0.2 to 0.5	0.371
Bp (posterior edge)	–2.0	(1.2)	322	–2.1	(1.1)	326	–0.03	–0.21 to 0.15	0.737	–2.1	(1.2)	299	–2.0	(1.2)	290	0.13	–0.1 to 0.3	0.196
TVL	8.1	(1.2)	320	8.2	(1.3)	318	0.12	–0.07 to 0.30	0.212	7.8	(1.2)	291	7.8	(1.2)	286	0.07	–0.1 to 0.3	0.503
Overall POP-Q stage																		
0	16.4%	56	341	14.2%	48	339	1.11	0.83 to 1.47	0.494	16.7%	51	305	14.0%	42	299	1.26	0.93 to 1.71	0.131
1	31.7%	108	341	33.3%	113	339				31.5%	96	305	28.4%	85	299			
2	44.9%	153	341	46.6%	158	339				44.3%	135	305	48.2%	144	299			
3	6.5%	22	341	5.6%	19	339				6.9%	21	305	8.4%	25	299			
4	0.6%	2	341	0.3%	1	339				0.7%	2	305	1.0%	3	299			
2b, 3 or 4	*13.9%*	*47*	*338*	*16.1%*	*54*	*336*	*1.12*	*0.79 to 1.60*	*0.519*	*15.5%*	*47*	*303*	*18.1%*	*54*	*298*	*1.14*	*0.80 to 1.62*	*0.471*

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

Adapted from Glazener CMA, Breeman S, Elders A, Hemming C, Cooper KG, Freeman RM, *et al.* Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT) [published online ahead of print 20 December 2016]. *Lancet* 2016. http://dx.doi.org/10.1016/S0140-6736(16)31596-3.[61] This is an open access article distributed under a CC BY 4.0 license (http://creativecommons.org/licenses/by/4.0/), which permits use of the work without further permission provided the original work is fully attributed. © 2016 The Author(s). Published by Elsevier Ltd.

If it was related to the initial prolapse surgery, a hospital readmission was automatically counted as a SAE. Surgery for recurrence of prolapse (repeat if same compartment, further surgery if in the opposite compartment), or for continence surgery, was differentiated from readmission for complications related to prolapse surgery, such as bleeding, infection and mesh removal (*Table 31*).

Readmission (not related to mesh exposure or further surgery for prolapse or incontinence)

The overall rate of readmission was low, and there was no significant difference between the randomised groups (see *Table 31*). The rate in the first 6 months, ranging from 2.7% to 4.2% (see *Table 31*), was mostly related to adverse effects, whereas after that time the rate reduced (1.0–1.8%) and readmissions were more likely to be related to treatment failure than adverse effects. There were no statistically significant differences between the randomised groups in either trial (see *Table 31*).

Treatment for repeat or further prolapse

Thirty women (from all the randomised groups) reported that they had had further prolapse surgery in the first year and another 50 women had more prolapse surgery in the second year: a total of 74 women. Six women had surgery in both years. Of the 1073 randomised women who completed questionnaires at both 1 year and 2 years, 66 had further prolapse surgery, making a total further surgery rate of 6.2% (see *Table 31*). Similarly, 50 of 837 (6.0%) of the cohort women had undergone further prolapse surgery. Overall, there was no statistically significant difference between the randomised groups in either trial in the number of women who were having further prolapse surgery at 1 year or 2 years (see *Table 31*); for example:

1. In trial 1, comparing the number of women who had further prolapse surgery in the first year in the standard repair group (1.5%) with synthetic mesh inlay (3.1%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), RR 1.99, 95% CI 0.76 to 5.24.
2. In trial 2, comparing the number of women who had further prolapse surgery in the first year in the standard repair group (2.0%) with biological graft (3.0%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), RR 1.44, 95% CI 0.56 to 3.73.

In the second year, more women received another prolapse repair:

1. In trial 1, comparing the number of women who had further prolapse surgery in the second year in the standard repair group (4.6%) with synthetic mesh inlay (4.4%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1B (two-way randomisation), RR 0.94, 95% CI 0.47 to 1.88.
2. In trial 2, comparing the number of women who had further prolapse surgery in the second year in the standard repair group (5.0%) with biological graft (5.0%), adjusted for baseline values and based on data only from women in stratum 1A (three-way randomisation) and stratum 1C (two-way randomisation), RR 0.99, 95% CI 0.49 to 1.98.

Few women required other treatment, such as pessaries or physiotherapy for persistent or recurrent prolapse symptoms, and there were no differences between the randomised groups in either trial regarding further use of services (also see *Chapter 5*). The data from the cohort women were similar.

Treatment for urinary incontinence and other bladder problems

Fourteen women had continence surgery in the first year, and a further 16 in the second year (one had continence surgery in both years): a total of 29 women. Of the 1073 randomised women who completed questionnaires at both years, 26 had continence surgery, thus a rate of 2.4%. Similarly, 15 of 837 (1.8%) of the cohort women had had repeat continence surgery. However, around 30% of women were using absorbent pads for urine leakage, and just under 10% were using drugs for urine problems, with similar proportions among the cohort women. Twelve women were using intermittent catheterisation for

TABLE 31 Further treatment required within first and second years: Primary trial

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									
Further treatment	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
6-month outcomes																					
Number of women at 6 months	*N* = 398			*N* = 381						*N* = 338			*N* = 335						*N* = 966		
Readmitted (0–6 months)	2.8%	11[a]	398	3.1%	12[b]	381	1.15	0.51 to 2.57	0.738	2.7%	9[c]	338	4.2%	14[d]	335	1.54	0.68 to 3.51	0.304	3.3%	32[e]	966
1-year outcomes																					
Number of women at 1 year	*N* = 395			*N* = 389						*N* = 342			*N* = 337						*N* = 972		
Readmitted (6–12 months)	1.0%	4[f]	395	1.3%	5[g]	389	1.32	0.36 to 4.81	0.677	1.2%	4[h]	342	1.8%	6[i]	337	1.67	0.48 to 5.79	0.416	0.7%	7[j]	972
New prolapse surgery	1.5%	6	395	3.1%	12	389	1.99	0.76 to 5.24	0.163	2.0%	7	342	3.0%	10	337	1.44	0.56 to 3.73	0.451	2.7%	26	972
Same compartment	0.8%	3	395	2.1%	8	389	2.55	0.68 to 9.53	0.163	1.5%	5	342	1.5%	5	337	0.98	0.29 to 3.34	0.976	0.9%	9	972
Different compartment	0.8%	3	395	1.0%	4	389	1.35	0.31 to 5.96	0.692	0.6%	2	342	1.5%	5	337	2.50	0.49 to 12.74	0.269	1.7%	17	972
Waiting for prolapse surgery	1.5%	6	395	0.5%	2	389	0.33	0.07 to 1.65	0.178	1.5%	5	342	1.2%	4	337	0.82	0.22 to 3.01	0.761	1.5%	15	972
Continence surgery	1.3%	5	395	0.5%	2	389	0.40	0.08 to 2.04	0.269	0.6%	2	342	2.1%	7	337	3.49	0.73 to 16.66	0.116	0.9%	9	972
Waiting for continence surgery	0.3%	1	395	0.5%	2	389	2.13	0.19 to 23.50	0.536	0.9%	3	342	0.3%	1	337	0.32	0.03 to 3.10	0.328	0.4%	4	972
Stitches removed	1.6%	6	381	1.1%	4	371	0.69	0.20 to 2.43	0.565	2.5%	8	326	3.7%	12	322	1.53	0.64 to 3.67	0.344	2.9%	27	938

continued

TABLE 31 Further treatment required within first and second years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft											
Further treatment	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value	CC1		
Any mesh complication	0.5%	2	430	7.4%	32	435				0.5%	2	367	0.5%	2	368				0.8%	9	1126
Surgical removal	0.5%	2	430	5.3%	23	435				0.5%	2	367	0.3%	1	368				0.7%	7	1126
Conservative treatment	0.0%	0	430	1.8%	8	435				0.0%	0	367	0.0%	0	368				0.1%	1	1126
No treatment	0.0%	0	430	0.2%	1	435				0.0%	0	367	0.3%	1	368				0.1%	1	1126
De novo	0.2%	1	430	6.2%	27	435				0.0%	0	367	0.0%	0	368				0.3%	3	1126
Concomitant	0.2%	1	430	1.1%	5	435				0.5%	2	367	0.5%	2	368				0.5%	6	1126
Treatment for prolapse at 1 year																					
Medicines for prolapse	12.9%	50	387	17.6%	67	381	1.36	0.97 to 1.89	0.075	15.5%	52	336	18.9%	62	328	1.23	0.88 to 1.71	0.235	15.6%	149	956
Oestrogens	13.4%	53	395	17.5%	68	389	1.32	0.95 to 1.83	0.100	14.3%	49	342	18.1%	61	337	1.26	0.89 to 1.78	0.185	12.3%	120	972
Ring pessary	3.3%	13	395	2.1%	8	389	0.61	0.26 to 1.46	0.269	2.3%	8	342	2.1%	7	337	0.88	0.32 to 2.41	0.811	2.1%	20	972
Shelf pessary	2.5%	10	395	0.8%	3	389	0.30	0.08 to 1.07	0.063	1.5%	5	342	1.5%	5	337	0.94	0.28 to 3.22	0.925	1.3%	13	972
Physiotherapy	6.3%	24	380	8.6%	32	370	1.36	0.82 to 2.27	0.232	6.7%	22	330	8.2%	27	328	1.22	0.71 to 2.10	0.462	8.5%	81	948
GP for prolapse	23.6%	91	385	26.5%	100	378	1.12	0.88 to 1.43	0.341	27.5%	92	334	29.1%	95	327	1.06	0.83 to 1.35	0.638	24.3%	230	946
Practice nurse	3.9%	15	382	6.5%	25	382	1.68	0.90 to 3.12	0.104	4.0%	13	329	5.8%	19	326	1.45	0.73 to 2.88	0.293	7.1%	67	942
GOPD	29.2%	112	383	37.1%	138	372	1.25	1.02 to 1.53	0.031	29.0%	97	334	32.9%	108	328	1.12	0.89 to 1.41	0.338	32.1%	304	946

Further treatment	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Treatment for urinary problems at 1 year																					
Pads	28.0%	109	389	31.3%	120	384	1.11	0.89 to 1.37	0.347	30.8%	104	338	28.2%	93	330	0.92	0.73 to 1.16	0.483	28.8%	275	956
Permanent catheter	0.3%	1	375	0.5%	2	369	1.83	0.17 to 20.02	0.621	0.3%	1	322	0.0%	0	320	N/A	N/A	N/A	0.2%	2	927
Intermittent catheter	1.1%	4	372	1.4%	5	367	1.24	0.34 to 4.56	0.749	0.9%	3	318	1.9%	6	321	2.05	0.52 to 7.98	0.302	1.4%	13	927
Drugs for UI	7.1%	28	395	8.5%	33	389	1.18	0.73 to 1.90	0.503	6.7%	23	342	8.9%	30	337	1.36	0.81 to 2.29	0.240	8.5%	83	972
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Readmitted (12–24 months)	0.9%	3[k]	348	0.0%	0	343	N/A	N/A	N/A	0.7%	2[l]	299	1.3%	4[m]	300	1.95	0.36 to 10.56	0.437	0.6%	5[n]	847
New prolapse surgery	4.6%	16	348	4.4%	15	343	0.94	0.47 to 1.88	0.869	5.0%	15	299	5.0%	15	300	0.99	0.49 to 1.98	0.976	3.4%	29	848
Same compartment	2.6%	9	348	2.0%	7	343	0.79	0.30 to 2.11	0.641	2.3%	7	299	2.7%	8	300	1.13	0.41 to 3.06	0.817	1.4%	12	848
Different compartment	2.0%	7	348	2.3%	8	343	1.14	0.42 to 3.10	0.799	2.7%	8	299	2.3%	7	300	0.86	0.32 to 2.33	0.764	2.0%	17	848
Waiting for prolapse surgery	0.9%	3	348	0.3%	1	343	0.34	0.04 to 3.27	0.351	0.7%	2	299	0.0%	0	300	N/A	N/A	N/A	0.1%	1	848
Continence surgery	1.1%	4	348	1.5%	5	343	1.28	0.35 to 4.73	0.714	2.3%	7	299	1.3%	4	300	0.56	0.17 to 1.90	0.353	0.8%	7	830
Waiting for continence surgery	0.0%	0	348	0.0%	0	343	N/A	N/A	N/A	0.0%	0	299	0.0%	0	300	N/A	N/A	N/A	0.2%	2	848
Stitches removed	0.0%	0	339	0.9%	3	331	N/A	N/A	N/A	0.0%	0	293	0.3%	1	291	N/A	N/A	N/A	0.2%	2	848

continued

TABLE 31 Further treatment required within first and second years: Primary trial (*continued*)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
Further treatment	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Any mesh complication	0.2%	1	430	5.7%	25	435				0.3%	1	367	0.3%	1	368				0.2%	2	1126
Surgical removal	0.0%	0	430	3.9%	17	435				0.0%	0	367	0.0%	0	368				0.2%	2	1126
Conservative	0.2%	1	430	0.9%	4	435				0.3%	1	367	0.0%	0	368				0.0%	0	1126
No treatment	0.0%	0	430	0.9%	4	435				0.0%	0	367	0.3%	1	368				0.0%	0	1126
De novo	0.0%	0	430	5.3%	23	435				0.0%	0	367	0.0%	0	368				0.1%	1	1126
Concomitant	0.2%	1	430	0.5%	2	435				0.0%	0	367	0.3%	1	368				0.1%	1	1126
Treatment for prolapse at 2 years																					
Medicines for prolapse	11.1%	38	341	11.0%	37	337	0.95	0.62 to 1.44	0.797	14.6%	43	295	12.5%	37	296	0.85	0.56 to 1.27	0.419	10.6%	88	834
Oestrogens	11.8%	41	348	14.9%	51	343	1.25	0.85 to 1.83	0.249	15.1%	45	299	16.3%	49	300	1.08	0.75 to 1.57	0.672	11.4%	97	848
Ring pessary	3.2%	11	348	1.7%	6	343	0.55	0.21 to 1.47	0.235	2.0%	6	299	3.3%	10	300	1.67	0.62 to 4.52	0.311	2.2%	19	848
Shelf pessary	1.7%	6	348	0.9%	3	343	0.44	0.11 to 1.75	0.242	2.3%	7	299	1.7%	5	300	0.66	0.21 to 2.03	0.468	1.4%	12	848
Physiotherapy	5.6%	19	342	7.5%	25	333	1.34	0.75 to 2.38	0.324	5.2%	15	290	6.8%	20	293	1.27	0.67 to 2.43	0.461	6.0%	50	832
GP for prolapse	13.6%	46	337	15.5%	52	335	1.15	0.80 to 1.65	0.459	12.2%	36	294	13.2%	38	288	1.06	0.70 to 1.62	0.775	14.2%	116	819
Practice nurse	3.3%	11	336	2.7%	9	330	0.82	0.34 to 1.95	0.648	2.7%	8	292	2.1%	6	289	0.75	0.27 to 2.14	0.595	3.2%	26	817
GOPD	15.2%	52	342	17.4%	58	333	1.14	0.81 to 1.60	0.461	15.5%	46	296	17.7%	52	293	1.13	0.79 to 1.61	0.519	13.1%	108	827

Further treatment	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
Treatment for urinary problems at 2 years																					
Pads	26.9%	92	342	28.6%	97	339	1.07	0.84 to 1.36	0.588	27.3%	81	297	25.5%	76	298	0.94	0.72 to 1.23	0.659	28.1%	233	830
Permanent catheter	0.0%	0	341	0.0%	0	331	N/A	N/A	N/A	0.0%	0	295	0.0%	0	291	N/A	N/A	N/A	0.2%	2	823
Intermittent catheter	1.2%	4	339	1.2%	4	332	1.00	0.25 to 3.93	0.996	1.4%	4	293	1.4%	4	291	0.97	0.25 to 3.82	0.962	1.6%	13	826
Drugs for UI	6.6%	23	348	9.3%	32	343	1.39	0.83 to 2.31	0.212	8.7%	26	299	8.3%	25	300	0.94	0.56 to 1.59	0.818	7.4%	63	848

GOPD, Gynaecology Outpatients Department; N/A, not applicable.
a Reasons for readmission (standard; 0–6 months): bleeding (2), retention (6), infection (2), pain (1).
b Reasons for readmission (synthetic; 0–6 months): bleeding (2), retention (3), adhesions (2), loosening of tape (1), infection (2), constipation (1), other (1).
c Reasons for readmission (standard; 0–6 months): retention (5), infection (3), constipation (1).
d Reasons for readmission (biological; 0–6 months): bleeding (2), retention (4), adhesions (1), loosening of tape (1), infection (4), constipation (1), pain (1).
e Reasons for readmission (CC1; 0–6 months): bleeding (4), retention (2), adhesions (4), revision prolapse surgery (Fenton's) (2), infection (11), constipation (3), pain (2), other (4).
f Reasons for readmission (standard; 6–12 months): loosening of tape (1), revision prolapse surgery (Fenton's) (2), other (1).
g Reasons for readmission (synthetic; 6–12 months): bleeding (1), retention (1), adhesions (1), revision prolapse surgery (Fenton's) (2).
h Reasons for readmission (standard; 6–12 months): loosening of tape (1), revision prolapse surgery (Fenton's) (2), other (1).
i Reasons for readmission (biological; 6–12 months): adhesions (2), revision prolapse surgery (Fenton's) (2), other (2).
j Reasons for readmission (CC1; 6–12 months): retention (1), adhesions (1), revision prolapse surgery (Fenton's) (1), infection (1), other (3).
k Reasons for readmission (standard; 12–24 months): adhesions (2), other (1).
l Reasons for readmission (standard; 12–24 months): adhesions (2).
m Reasons for readmission (biological; 12–24 months): adhesions (3), other (1).
n Reasons for readmission (CC1; 12–24 months): adhesions (2), infection (2), other (1).
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Readmission: Related to prolapse surgery (for complications). Readmission for new prolapse, incontinence or mesh complications surgery presented separately.

obstructed or incomplete voiding by 2 years, and 13 in the cohort. There were no statistically significant differences between the women in either trial, and the data from the cohort women were similar.

Treatment for mesh complications

In the synthetic mesh trial, there were 34 instances of serious adverse effects associated with mesh complications in the first year for randomised women, but only 25 women required surgery to remove part of the mesh, of whom two were in the standard group: 18 (72%) were asymptomatic and 16 (64%) had exposures of < 1 cm^2 (see *Table 31*). One of these women had total mesh removal within 2 weeks of surgery because of severe infection causing rejection. A further eight women (see *Table 31*) had conservative treatment only (such as local oestrogen, cautery with silver nitrate, or antibiotics) in the first year and one needed no treatment. In the second year, 26 women had a mesh complication (see *Table 31*), of whom 17 had surgical removal: 13 (76%) were asymptomatic and 10 (59%) had exposures of < 1 cm^2. Five received conservative treatment and another four required no treatment (see *Table 31*).

In the biological graft trial, four women had a mesh complication in the first year but all had concomitant synthetic mesh and only three required surgical intervention (none were symptomatic or had exposures of > 1 cm^2). Two women had a mesh complication in the second year but neither required surgical treatment.

The cumulative mesh complication rates over 2 years were 2 of 430 (0.5%) for standard repair (trial 1), 46 of 435 (10.6%) for mesh inlay and 2 of 368 (0.5%) for biological graft.

Satisfaction with treatment at 1 year and 2 years

Women reported that they took around 3 months to recover, with no differences between any of the randomised groups (*Table 32*). Over 80% of the women were very much or much better than before surgery, and similar proportions were completely or fairly satisfied. Over 90% of women would 'recommend the surgery to a friend'. The data were similar at 1 year and 2 years, suggesting that, on average, the positive benefits of surgery were sustained, with no statistically significant differences between the randomised groups, and the findings were similar among the cohort women (see *Table 32*). These data are in line with the clinical outcome data, supporting the positive benefits of prolapse surgery for the majority of women.

Analysis by treatment received

Post hoc analysis of the primary outcome measure, the POP-Q data and a selection of key secondary outcomes for the primary repair trials (trials 1 and 2) was undertaken following discussion at the collaborators' meetings on 17 October 2014 and 4 September 2015. This analysis compared randomised groups but used the actual type of prolapse repair that the women had received rather than the planned procedure to define the subgroups. Results are presented for all women who received prolapse surgery (*Table 33*), the subgroup of women who received an anterior repair only (*Table 34*), a posterior repair only (*Table 35*) and those who received both an anterior and posterior repair concomitantly (*Table 36*).

There were no significant differences in the POP-SS at 1 year between groups (standard repair vs. synthetic mesh or standard repair vs. biological graft) for any of the subgroups or for the combined group. For women who had an anterior repair only, the rate beyond the hymen for the anterior edge (POP-Q stage 2b or more) was 12.3% for standard compared with 13.3% for synthetic mesh and 15.4% for standard compared with 25.9% for biological graft. However, these differences were not significant (see *Table 34*). Similarly, for women who had a posterior repair only, the rate beyond the hymen for the posterior edge was 4.0% for standard compared with 5.9% for synthetic mesh, and 4.6% for standard compared with 5.1% for biological graft, and these differences were not significant (see *Table 35*). There were no significant differences between groups in any of the other outcome measures, except serious mesh complications.

TABLE 32 Recovery time and satisfaction with surgery: Primary trial

Recovery/ satisfaction	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
1-year outcomes																					
Number of women at 1 year	*N* = 368			*N* = 362						*N* = 319			*N* = 316						*N* = 893		
Time to recovery (months)	3.0	(1.8)	342	3.0	(1.7)	342	0.00	–0.27 to 0.26	0.990	3.1	(1.8)	296	3.3	(1.9)	293	0.28	–0.03 to 0.58	0.073	3.1	(2.1)	828
Prolapse compared with before surgery at 1 year																					
Very much better	57.7%	203	352	56.2%	199	354	0.93	0.69 to 1.26	0.655	57.6%	174	302	52.8%	160	303	0.81	0.58 to 1.12	0.198	51.0%	439	860
Much better	24.1%	85	352	26.8%	95	354				24.5%	74	302	25.7%	78	303				28.6%	246	860
A little better	9.7%	34	352	9.3%	33	354				8.9%	27	302	8.6%	26	303				9.9%	85	860
No change	2.8%	10	352	3.4%	12	354				3.6%	11	302	7.3%	22	303				5.6%	48	860
A little worse	3.1%	11	352	1.4%	5	354				3.3%	10	302	2.6%	8	303				1.4%	12	860
Much worse	2.0%	7	352	2.5%	9	354				1.3%	4	302	2.3%	7	303				2.1%	18	860
Very much worse	0.6%	2	352	0.3%	1	354				0.7%	2	302	0.7%	2	303				1.4%	12	860
Satisfaction with surgery at 1 year																					
Completely satisfied	58.0%	203	350	58.9%	208	353	1.03	0.76 to 1.40	0.852	58.4%	177	303	56.5%	170	301	0.90	0.65 to 1.26	0.548	50.5%	434	860
Fairly satisfied	30.0%	105	350	26.1%	92	353				28.7%	87	303	27.2%	82	301				34.9%	300	860
Fairly dissatisfied	3.1%	11	350	7.1%	25	353				4.3%	13	303	5.3%	16	301				4.3%	37	860
Very dissatisfied	5.4%	19	350	4.8%	17	353				5.0%	15	303	6.6%	20	301				6.2%	53	860
Not sure	3.4%	12	350	3.1%	11	353				3.6%	11	303	4.3%	13	301				4.2%	36	860
Recommend to a friend	90.2%	312	346	90.9%	310	341	1.01	0.96 to 1.06	0.604	90.2%	267	296	90.3%	262	290	1.01	0.95 to 1.07	0.751	90.3%	758	839

continued

TABLE 32 Recovery time and satisfaction with surgery: Primary trial (*continued*)

Recovery/ satisfaction	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft									CC1		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value			
2-year outcomes																					
Number of women at 2 years	*N* = 348			*N* = 343						*N* = 299			*N* = 300						*N* = 848		
Prolapse compared with before surgery at 2 years																					
Very much better	56.6%	194	343	53.3%	180	338	0.88	0.65 to 1.20	0.425	57.5%	169	294	49.3%	146	296	0.73	0.52 to 1.01	0.058	50.3%	419	833
Much better	23.3%	80	343	26.0%	88	338				23.1%	68	294	27.7%	82	296				26.2%	218	833
A little better	10.8%	37	343	13.9%	47	338				10.2%	30	294	9.1%	27	296				10.9%	91	833
No change	5.2%	18	343	3.3%	11	338				5.1%	15	294	5.7%	17	296				6.5%	54	833
A little worse	1.7%	6	343	1.8%	6	338				2.7%	8	294	5.4%	16	296				2.5%	21	833
Much worse	0.9%	3	343	1.2%	4	338				0.3%	1	294	1.0%	3	296				2.3%	19	833
Very much worse	1.5%	5	343	0.6%	2	338				1.0%	3	294	1.7%	5	296				1.3%	11	833
Satisfaction with surgery at 2 years																					
Completely satisfied	56.3%	193	343	54.0%	183	339	0.91	0.67 to 1.25	0.570	58.5%	172	294	54.2%	161	297	0.86	0.61 to 1.20	0.365	52.2%	434	832
Fairly satisfied	28.9%	99	343	34.2%	116	339				28.9%	85	294	28.3%	84	297				30.8%	256	832
Fairly dissatisfied	5.5%	19	343	4.1%	14	339				4.8%	14	294	6.4%	19	297				6.1%	51	832
Very dissatisfied	5.5%	19	343	2.7%	9	339				4.4%	13	294	6.7%	20	297				6.0%	50	832
Not sure	3.8%	13	343	5.0%	17	339				3.4%	10	294	4.4%	13	297				4.9%	41	832
Recommend to a friend	90.5%	304	336	89.4%	295	330	0.98	0.93 to 1.03	0.413	91.3%	262	287	87.0%	247	284	0.95	0.90 to 1.01	0.104	87.3%	705	808

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Satisfaction with surgery

How is prolapse compared with before surgery? Very much better = cured [1]; much or a little better (or very much better) = improved or cured [< 4]; no change or worse = failed [> 3].

Satisfied with results of operation? Completely satisfied = cured [1]; fairly satisfied = improved or cured [1 or 2]; fairly or very dissatisfied = failed [3 or 4]; not sure = separate category [5].

TABLE 33 Analysis by treatment received (all women who received prolapse surgery)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
All women who received prolapse surgery	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
POP-SS at 12 months	5.4	(5.5)	395	5.5	(5.1)	389	0.00	–0.70 to 0.71	0.989	5.5	(5.6)	342	5.6	(5.6)	337	–0.15	–0.93 to 0.63	0.706
Leading edge (2b or more)	13.9%	47	339	16.0%	54	337	1.12	0.79 to 1.60	0.522	15.5%	47	304	18.0%	54	300	1.13	0.79 to 1.61	0.502
Anterior edge (2b or more)	11.2%	38	339	12.5%	42	337	1.19	0.78 to 1.81	0.424	12.5%	38	304	15.7%	47	300	1.28	0.87 to 1.89	0.213
Posterior edge (2b or more)	3.0%	10	338	4.1%	14	338	1.40	0.63 to 3.08	0.409	3.3%	10	304	3.4%	10	297	1.00	0.43 to 2.35	0.995
Ba (anterior edge)	–1.3	(1.6)	324	–1.3	(1.6)	328	0.05	–0.18 to 0.28	0.653	–1.3	(1.7)	300	–1.2	(1.7)	295	0.12	–0.1 to 0.4	0.358
C (cervix/vault)	–6.0	(2.1)	319	–6.0	(2.3)	321	–0.01	–0.35 to 0.32	0.939	–5.8	(1.9)	293	–5.7	(2.1)	294	0.15	–0.2 to 0.5	0.383
Bp (posterior edge)	–2.0	(1.2)	323	–2.1	(1.1)	327	–0.03	–0.21 to 0.15	0.720	–2.1	(1.2)	300	–2.0	(1.2)	292	0.12	–0.1 to 0.3	0.230
Repeat prolapse surgery (any) within 12 months	1.5%	6	395	3.1%	12	389	1.96	0.74 to 5.16	0.174	2.0%	7	342	3.0%	10	337	1.40	0.54 to 3.63	0.488
Repeat same compartment	0.8%	3	395	2.1%	8	389	2.50	0.67 to 9.35	0.172	1.5%	5	342	1.5%	5	337	0.95	0.28 to 3.23	0.933
Repeat different compartment	0.8%	3	395	1.0%	4	389	1.35	0.30 to 5.96	0.694	0.6%	2	342	1.5%	5	337	2.45	0.48 to 12.47	0.281

continued

TABLE 33 Analysis by treatment received (all women who received prolapse surgery) (*continued*)

All women who received prolapse surgery	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
New continence surgery	1.3%	5	395	0.5%	2	389	0.40	0.08 to 2.02	0.265	0.6%	2	342	2.1%	7	337	3.34	0.70 to 15.94	0.130
Any SAE within 12 months	7.2%	31	430	7.8%	34	435	1.08	0.68 to 1.72	0.730	6.3%	23	367	9.8%	36	368	1.57	0.95 to 2.59	0.076
Serious mesh exposure within 12 months	0.5%	2	430	7.4%	32	435				0.5%	2	367	0.5%	2	368			

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome.

Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 34 Analysis by treatment received (women who received an anterior repair)

Women who received an anterior repair	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
POP-SS at 12 months	4.7	(4.8)	172	5.3	(5.5)	173	0.37	–0.68 to 1.42	0.485	5.0	(5.1)	127	5.4	(5.9)	122	0.23	–1.11 to 1.57	0.740
Leading edge (2b or more)	15.8%	23	146	16.7%	25	150	1.01	0.61 to 1.66	0.982	19.7%	23	117	26.9%	29	108	1.11	0.76 to 1.62	0.587
Anterior edge (2b or more)	12.3%	18	146	13.3%	20	150	0.98	0.53 to 1.80	0.944	15.4%	18	117	25.9%	28	108	1.16	0.90 to 1.49	0.256
Posterior edge (2b or more)	3.4%	5	145	4.0%	6	150	1.12	0.35 to 3.59	0.846	4.3%	5	117	2.8%	3	107	0.75	0.18 to 3.11	0.695
Ba (anterior edge)	–1.2	(1.7)	139	–1.3	(1.6)	147	–0.15	–0.49 to 0.19	0.381	–1.0	(1.7)	115	–0.6	(1.8)	108	0.23	–0.2 to 0.7	0.271
C (cervix/vault)	–6.1	(2.1)	136	–6.0	(2.4)	143	0.00	–0.51 to 0.51	0.997	–6.1	(1.7)	113	–5.2	(2.4)	108	0.56	0 to 1.1	0.046
Bp (posterior edge)	–2.0	(1.1)	139	–2.0	(1.1)	146	–0.02	–0.27 to 0.23	0.877	–2.1	(1.0)	115	–2.0	(1.1)	107	0.17	–0.1 to 0.4	0.222
Repeat prolapse surgery (any) within 12 months	1.7%	3	172	3.5%	6	173	1.91	0.48 to 7.52	0.355	1.6%	2	127	2.5%	3	122	1.53	0.26 to 8.97	0.640
Repeat same compartment	1.2%	2	172	2.9%	5	173	2.37	0.47 to 12.06	0.299	1.6%	2	127	2.5%	3	122	1.53	0.26 to 8.97	0.640
Repeat different compartment	0.6%	1	172	0.6%	1	173	0.99	0.06 to 15.82	0.997	0.0%	0	127	0.0%	0	122	N/A	N/A	N/A
New continence surgery	1.2%	2	172	0.6%	1	173	0.40	0.08 to 2.02	0.265	0.8%	1	127	1.6%	2	122	2.08	0.19 to 22.43	0.546
Any SAE within 12 months	8.2%	15	184	4.3%	8	187	0.52	0.23 to 1.19	0.123	6.8%	9	132	10.6%	14	132	1.55	0.70 to 3.46	0.281
Serious mesh exposure within 12 months	1.1%	2	184	7.5%	14	187	6.75	1.55 to 29.41	0.011	0.8%	1	132	0.0%	0	132	N/A	N/A	N/A

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.
POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 35 Analysis by treatment received (women who received a posterior repair)

	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
Women who received a posterior repair	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
POP-SS at 12 months	6.4	(6.3)	116	5.7	(4.9)	116	–0.56	–1.90 to 0.79	0.415	6.5	(6.3)	97	6.0	(5.9)	112	–1.06	–2.59 to 0.47	0.172
Leading edge (2b or more)	13.1%	13	99	18.0%	18	100	1.69	0.83 to 3.47	0.149	13.8%	12	87	8.1%	8	99	0.62	0.26 to 1.49	0.282
Anterior edge (2b or more)	10.1%	10	99	12.0%	12	100	1.57	0.69 to 3.58	0.283	10.3%	9	87	3.0%	3	99	0.40	0.11 to 1.44	0.160
Posterior edge (2b or more)	4.0%	4	99	5.9%	6	101	2.36	0.57 to 9.82	0.238	4.6%	4	87	5.1%	5	99	1.05	0.30 to 3.74	0.935
Ba (anterior edge)	–1.6	(1.5)	95	–1.5	(1.6)	96	0.17	–0.32 to 0.66	0.490	–1.8	(1.6)	86	–1.8	(1.3)	97	0.05	–0.4 to 0.5	0.807
C (cervix/vault)	–6.2	(2.1)	95	–6.2	(2.2)	95	–0.01	–0.65 to 0.62	0.967	–6.0	(2.0)	86	–6.1	(1.5)	97	–0.15	–0.7 to 0.4	0.612
Bp (posterior edge)	–1.9	(1.4)	95	–2.1	(1.3)	96	–0.13	–0.56 to 0.30	0.544	–2.0	(1.5)	86	–1.9	(1.3)	96	0.08	–0.3 to 0.5	0.698
Repeat prolapse surgery (any) within 12 months	1.7%	2	116	1.7%	2	116	0.96	0.14 to 6.76	0.965	3.1%	3	97	3.6%	4	112	1.10	0.25 to 4.83	0.898
Repeat same compartment	0.0%	0	116	0.0%	0	116	N/A	N/A	N/A	1.0%	1	97	0.0%	0	112	N/A	N/A	N/A
Repeat different compartment	1.7%	2	116	1.7%	2	116	0.96	0.14 to 6.76	0.965	2.1%	2	97	3.6%	4	112	1.62	0.30 to 8.70	0.574
New continence surgery	0.0%	0	116	0.0%	0	116	N/A	N/A	N/A	0.0%	0	97	1.8%	2	112	N/A	N/A	N/A
Any SAE within 12 months	4.0%	5	125	10.2%	13	127	2.98	1.09 to 8.11	0.123	2.9%	3	103	6.8%	8	117	2.28	0.62 to 8.36	0.214
Serious mesh exposure within 12 months	0.0%	0	125	7.1%	9	127				1.0%	1	103	0.9%	1	117			

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.
POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 36 Analysis by treatment received (women who received an anterior and a posterior repair)

Women who received an anterior and a posterior repair	Trial 1: standard repair vs. synthetic mesh									Trial 2: standard repair vs. biological graft								
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Biological			Effect size	95% CI	*p*-value
POP-SS at 12 months	5.6	(5.9)	90	5.4	(4.9)	86	–0.22	–1.79 to 1.34	0.777	5.1	(5.3)	105	5.3	(4.9)	98	–0.07	–1.33 to 1.18	0.908
Leading edge (2b or more)	10.3%	8	78	11.7%	9	77	1.53	0.60 to 3.88	0.370	10.3%	9	87	19.5%	17	87	1.79	0.82 to 3.91	0.143
Anterior edge (2b or more)	9.0%	7	78	10.4%	8	77	2.03	0.76 to 5.39	0.156	9.2%	8	87	18.4%	16	87	2.17	0.95 to 4.91	0.064
Posterior edge (2b or more)	1.3%	1	78	2.6%	2	77	1.49	0.14 to 15.77	0.743	1.1%	1	87	2.4%	2	85	1.49	0.15 to 15.17	0.737
Ba (anterior edge)	–1.3	(1.6)	74	–1.1	(1.7)	75	0.23	–0.23 to 0.68	0.328	–1.3	(1.5)	86	–1.1	(1.8)	84	0.12	–0.4 to 0.6	0.639
C (cervix/vault)	–5.6	(1.8)	72	–5.6	(2.5)	73	–0.03	–0.85 to 0.80	0.951	–5.5	(1.6)	81	–5.7	(2.1)	83	–0.17	–0.8 to 0.5	0.611
Bp (posterior edge)	–2.2	(1.1)	73	–2.1	(1.2)	75	0.02	–0.37 to 0.40	0.935	–2.3	(1.0)	86	–2.2	(1.4)	83	0.01	–0.4 to 0.4	0.961
Repeat prolapse surgery (any) within 12 months	1.1%	1	90	3.5%	3	86	2.48	0.27 to 23.10	0.424	1.9%	2	105	2.0%	2	98	1.06	0.15 to 7.43	0.954
Repeat same compartment	1.1%	1	90	3.5%	3	86	2.48	0.27 to 23.10	0.424	1.9%	2	105	2.0%	2	98	1.06	0.15 to 7.43	0.954
Repeat different compartment	0.0%	0	90	0.0%	0	86	N/A	N/A	N/A	0.0%	0	105	0.0%	0	98	N/A	N/A	N/A
New continence surgery	1.1%	1	90	1.2%	1	86	0.40	0.08 to 2.02	0.265	1.0%	1	105	3.1%	3	98	2.80	0.30 to 26.40	0.369
Any SAE within 12 months	10.2%	10	98	12.9%	12	93	1.31	0.60 to 2.88	0.494	10.0%	11	110	13.0%	14	108	1.37	0.65 to 2.90	0.412
Serious mesh exposure within 12 months	0.0%	0	98	9.7%	9	93				0.0%	0	110	0.9%	1	108			

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.
POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

Subgroup analysis

The results of the subgroup analyses are summarised in *Table 37*. There are no significant subgroup interaction effects from any of the planned subgroup analyses.

Sensitivity analysis

Several sensitivity analyses were carried out on the primary outcome (POP-SS at 1 year) to examine the impact of missing data under varying assumptions and test the assumption of treating unanswered individual Pelvic Organ Prolapse Symptom scale items as asymptomatic (*Table 38*). In the main analysis comparing standard repair with synthetic mesh, the point estimate for the effect size was 0.00, and this estimate varied between –0.17 and 0.29 in the sensitivity analyses. In the comparison between standard repair and biological graft, the point estimate in the main analysis was –0.15, which varied between –0.19 and 0.18 in the sensitivity analyses (see *Table 38*). None of the sensitivity analyses showed any significant difference between groups and, therefore, the results of the sensitivity analyses are consistent with the main analysis.

Missing POP-SSs in the standard repair arm would need to be 11 points higher than their missing-at-random imputed values for there to be a significant benefit for synthetic mesh or missing POP-SSs would need to be seven points higher in the synthetic mesh arm for there to be a significant benefit for standard repair. Similarly, missing POP-SSs would need to be nine points higher for standard repair for there to be a significant benefit for biological graft or missing POP-SSs would need to be eight points higher for biological graft for there to be a significant benefit for standard repair.

Discussion

Summary of findings

Effectiveness

There were no statistically significant differences at 1 year in the primary clinical outcomes after prolapse surgery using native tissue, synthetic non-absorbable mesh or biological graft material to reinforce the repair. In particular, the CI around the primary measure of women's symptoms, the POP-SS, was smaller than the minimally important clinical difference of two,[23] suggesting that it would be unlikely that there was a clinically significant difference between the groups in both trials. There were also no important differences in the secondary clinical or objective outcomes, or in the proportion of women requiring further treatment in either of the trials.

Adverse effects

The overall incidence of serious adverse effects was low, and there was no excess in the mesh or graft groups, other than mesh related, compared with the standard repair groups in either trial. Although women could have a mesh-related complication only if they received mesh, in about one-third of cases this was treated conservatively.

In the synthetic mesh trial, some women had mesh complications but most were small mesh exposures measuring < 1 cm^2 and many were asymptomatic or did not require treatment. Although there was no evidence of difference in other adverse effects up to 2 years after surgery, synthetic mesh use did result in additional surgical procedures for removal of a small part of the mesh, which may be considered to be an unnecessary risk.

Only six women in the biological graft trial had mesh exposure, all in women who had concomitant procedures with synthetic mesh; three of them required surgical correction.

TABLE 37 Subgroup analyses of Pelvic Organ Prolapse Symptom scale at 1 year

	Trial 1							Trial 2						
	Standard repair			Synthetic mesh			Interaction test:	Standard repair			Biological graft			Interaction test:
Subgroup	Mean	SD	*n*	Mean	SD	*n*	*p*-value	Mean	SD	*n*	Mean	SD	*n*	*p*-value
Age group (years)														
< 60	6.0	5.8	188	6.4	5.7	185	0.397	5.9	5.7	161	6.1	5.9	159	0.865
≥ 60	4.9	5.2	207	4.6	4.4	204		5.2	5.5	181	5.2	5.3	178	
Type of planned prolapse repair														
Anterior only	4.7	4.9	188	5.4	5.5	191	0.392	5.0	5.2	138	5.2	5.4	135	0.658
Posterior only	6.4	6.4	103	5.6	5.0	102		6.8	6.5	85	5.7	6.1	93	
Both	5.6	5.6	104	5.5	4.7	96		5.2	5.2	119	6.1	5.3	109	
Planned concomitant continence procedure														
Yes	5.7	4.7	38	5.9	5.3	41	0.658	5.8	4.7	40	6.2	6.5	39	0.106
No	5.4	5.6	357	5.4	5.1	348		5.5	5.7	302	5.6	5.5	298	
Planned concomitant upper prolapse procedure														
Yes	4.6	4.8	186	5.0	5.1		0.323	4.8	5.1	175	5.3	5.4	162	0.224
No	6.1	6.0	209	5.9	5.1	213		6.2	6.0	167	5.9	5.7	175	
Parity														
Zero to two deliveries	5.2	5.3	223	5.0	4.7	201	0.512	5.3	5.3	184	5.4	5.5	184	0.856
Three or more deliveries	5.6	5.9	171	5.9	5.5	187		5.8	5.9	158	5.9	5.7	153	

Dichotomous variables are presented as '% *n* *N*'.

TABLE 38 Sensitivity analyses of Pelvic Organ Prolapse Symptom scale at 1 year

	Trial 1: standard repair vs. synthetic mesh			Trial 2: standard repair vs. biological graft		
Analysis	Effect size	95% CI	*p*-value	Effect size	95% CI	*p*-value
Main analysis	0.00	–0.70 to 0.71	0.989	–0.15	–0.93 to 0.63	0.706
Assuming missing at random	0.08	–0.66 to 0.82	0.839	0.01	–0.77 to 0.79	0.985
Missing POP-SSs assumed to be 2 points higher	0.01	–0.76 to 0.77	0.985	0.03	–0.79 to 0.85	0.950
Missing POP-SSs assumed to be 2 points lower	–0.09	–0.85 to 0.67	0.818	–0.04	–0.86 to 0.78	0.922
Missing POP-SSs assumed to be 2 points higher in the standard repair arm only	–0.09	–0.83 to 0.66	0.821	–0.13	–0.91 to 0.65	0.745
Missing POP-SSs assumed to be 2 points lower in the standard repair arm only	0.24	–0.50 to 0.98	0.528	0.14	–0.64 to 0.93	0.717
Missing POP-SSs assumed to be 2 points higher in the mesh arm only	0.29	–0.46 to 1.03	0.448	0.18	–0.61 to 0.96	0.658
Missing POP-SSs assumed to be 2 points lower in the mesh arm only	–0.13	–0.88 to 0.61	0.722	–0.16	–0.95 to 0.62	0.686
Unanswered Pelvic Organ Prolapse Symptom scale items treated as missing	–0.17	–0.89 to 0.56	0.652	–0.19	–1.00 to 0.62	0.647

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome.

Cost-effectiveness

See *Chapter 5*.

Strengths and weaknesses

Strengths

The PROSPECT trial is the largest trial of the use of mesh or graft in prolapse surgery to date. It was powered to detect a clinically meaningful difference in the primary outcome, prolapse symptoms, in women who were having a first anterior or posterior prolapse operation. Owing to experience or availability of resources locally, some surgeons were not able to randomise between all three options, hence the comparison between standard and biological graft did not quite reach the expected sample size of 400. However, because of the high response rates we reached within 2% of our target at 1 year for the standard compared with synthetic comparison.

Generalisable because of the wide range of UK centres and gynaecologists

Women who enrolled in RCT1 and CC1 have been described and compared in *Chapter 3*; by and large, the populations were similar, suggesting that the findings from the randomised women will be generalisable to the larger population of women who were having prolapse surgery in the UK.

Data available separately for primary and secondary surgery

Our ability to differentiate between women who were having a first or a repeat procedure in a particular compartment ensured that our findings can be applied to the needs of specific categories of women. It is possible that women who require a repeat repair will present a greater anatomical challenge because of previous scarring and hence may require a different surgical approach (see *Chapter 6*).

Non-randomised cohort

Another strength was the inclusion of women who were not randomised. Data collection using the same questionnaires as the trial women demonstrated that our population was representative of the majority of women who were having prolapse surgery in the UK (see *Chapter 3*). Outcome data collected from the cohort women demonstrated that their outcomes were similar to those from the randomised women, thus ensuring generalisability of the findings. A further benefit was the ability to identify less common adverse effects.

Pragmatic nature of the research

One of the strengths of the trial was its pragmatic reflection of actual practice in a representative sample of UK prolapse surgeons across a large number of hospital settings, including a wide range of surgical techniques and types of mesh and graft. We did not standardise the surgical techniques used: surgeons varied in whether they placed the mesh under or over the fascia, and whether they repaired fascial defects or lateral detachment. Furthermore the operations were performed by a variety of staff, although primarily consultant surgeons. This was reflected in the range of concomitant surgery performed. Consultants were, however, more likely to operate on women who were randomised to mesh or graft than to standard repairs.

Validated outcome measures

We used validated outcome measures such as the Pelvic Organ Prolapse Symptom scale and ICI suite of instruments to measure women's symptoms of pelvic floor dysfunction, ensuring that our findings are comparable with other trials and can be combined within a meta-analysis.[23,26] We captured a wide range of adverse effects, and made efforts to verify these from alternative sources, such as hospital records, when possible. Essential missing data were actively sought from the women. Participants, outcome assessors and data entry clerks were blinded to randomisation and, as far as possible, to treatment actually received.

Weaknesses

The limitations of our study should be acknowledged. The large number of interventions and outcomes make it likely that some differences may have occurred by chance. However, the findings from all of the outcomes were remarkably consistent, and leave little room for doubt regarding the findings of the trials.

We have presented data from women who were having a first repair in the compartment requiring surgery, although around 10% of the women had undergone a previous repair in the opposite compartment. Thus, these results do not apply to women who were having repeat surgery in that compartment, who are presented in *Chapter 6*.

Because of the chronic and relapsing nature of prolapse, longer follow-up is required: the average time to a repeat operation is around 12 years.[4] Although we did not identify differences in the repeat surgery rate between the groups, it is likely that 2 years is too short a time scale to provide a definitive answer. We were able to identify complications, early recurrence and need for extra treatment, however. We have commenced follow-up for at least 6 years after surgery, and also plan electronic data linkage to capture outcomes from non-responders.

Pelvic Organ Prolapse Quantification stage (controversy over dividing up Stage 2)

The POP-Q system classes measurements from –1 cm inside the hymen to 1 cm as Stage 2.[27] We and other researchers[28] have arbitrarily used a measurement of > 0 cm to indicate objective failure, while recognising that women with worse findings may not have symptoms and, vice versa, women with objective 'cure' may still have prolapse symptoms. However, *Table 30* shows that the findings would have been the same whichever stage of prolapse was chosen as the cut-off.

Women with no prolapse at baseline/relationship between symptoms and objective findings

A small number of women were classed as having stage 0 or 1 on the POP-Q system before surgery. All of these women were symptomatic, and clearly their surgeons felt that prolapse surgery was indicated despite lack of objective measurable prolapse: in some cases there was evidence that the full descent had

not been measured. The lack of concordance between prolapse symptoms and objective prolapse descent has been noted previously.[62] It is still unclear why some women appeared to have surgery in the absence of measured descent; there may be a training issue.

We agree that although the primary purpose of surgery should be improvement in the woman's symptoms, if the woman has persistent symptoms but no prolapse it is difficult to justify repeat surgery.

Comparison with other research

The PROSPECT trial has shown that, in the first 2 years after surgery, there is no benefit to women who were having their first repair either in terms of prolapse symptoms or anatomical cure from the use of synthetic mesh or biological graft to reinforce a standard anterior or posterior repair. This is in stark contrast with the conclusions of the most recent Cochrane review,[18] which found both a reduction in the number of women with prolapse symptoms with synthetic mesh (29% vs. 21%, RR 1.44, 95% CI 1.15 to 1.80; six RCTs, including 930 women) and improved anatomical measurements (45% vs. 21%, RR 2.45, 95% CI 1.64 to 3.67; 11 RCTs, 1155 women).

On the other hand, our findings concur with the uncertainty of the evidence for a difference for biological grafts (RR for number of women with symptoms 1.03, 95% CI 0.61 to 1.75; 3 RCTs, 401 women; RR for objective failure 1.35, 95% CI 0.74 to 2.46; 6 RCTs, 565 women) but with narrower CIs. Given that surgical failures requiring repeat repair occur, on average, 12 years after initial surgery, longer-term follow-up is required to determine true effectiveness and other sequelae of mesh or graft insertion.

Importantly, complications from mesh insertion were similar in frequency to those reported in the Cochrane review,[18] and, in general, minor and easily resolved.

Differences in concomitant operations actually carried out in both trials were observed. More women had a vaginal hysterectomy in the standard arms than in the intervention arms but these differences were not significant. It is possible that knowledge of the allocated intervention influenced the surgery actually performed (so that if the woman was randomised to mesh or graft, she was less likely to have a concomitant hysterectomy). However, overall there were no substantial differences between the groups in the panel of operations that was carried out. This emphasises the importance of taking into consideration concomitant symptoms when managing women whose primary complaint is prolapse.

Summary

In both trials, the difference between the groups, and the size of the CI to either side, was considerably less than the prespecified minimally important clinical difference of two. The finding that more women appeared to have residual prolapse after mesh or graft repair than after standard repair was not statistically significant, and the difference was so small that it is not likely to be clinically significant. We conclude that although prolapse surgery was very effective in reducing women's prolapse symptoms, the use of synthetic mesh or biological graft did not provide additional benefit in women who were having their first repair.

Conclusions

There appears to be no benefit to women who were having their first prolapse repair from using synthetic mesh or biological graft to reinforce the repair, in terms of prolapse symptoms, anatomical cure of prolapse or non-mesh adverse effects. However, a minority of women required an additional surgical procedure to remove exposed mesh, which may be considered to be an unnecessary risk. This additional risk suggests that mesh should be used in the future only in the context of RCTs aimed at identifying benefit from modifying mesh type or insertion techniques or in defined categories of high-risk women.

Chapter 5 Health economics results: Primary trial

This chapter describes the within-trial cost–utility analysis of the randomised women who were having their first anterior or posterior prolapse repair (RCT1).

In this chapter, the data are presented as incremental cost per QALY gained over 2-year follow-up. The perspective of the analyses is primarily that of the UK NHS, with a supplementary analysis incorporating wider perspective costs, including participant travel costs, opportunity costs of time for participants and companions spent attending appointments, self-purchased health care and time off work as a result of prolapse symptoms. This latter analysis provides a wider scope on the economic consequences of prolapse surgery.

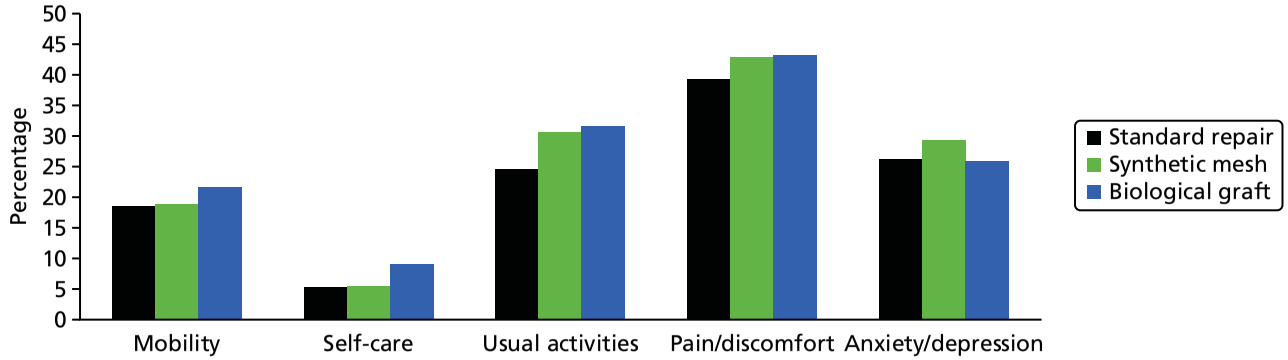
The base-case health-economic analysis is presented for complete case data for women who were randomised to the three-way comparison of standard repair, synthetic mesh and biological graft (i.e. all women randomised to RCT1A for the Primary trial (see *Chapter 2* for further information). The rationale for taking this approach for the economic analysis, and for taking a slightly different base-case approach to that of the statistical analysis of effect size, is that, in order to conduct a meaningful economic analysis and follow best practice economic evaluation procedures, all treatment options need to be considered together in a single analysis. This enables the exclusion of any treatment options that may be more costly and less effective than any other treatment alternative. The approach allows for the calculation and comparison of net benefits for all treatment strategies, to determine the strategy with the greatest probability of cost-effectiveness. Data presented for the estimation of incremental costs, QALYs and ICERs throughout the chapter are thus based on women randomised to RCT1A only. A sensitivity analysis reproduces the base-case cost-effectiveness analysis utilising all of the available data across the Primary trial. This considers the impact on results of considering two-way comparisons, thus making use of all of the data that are available for analysis.

The trial-based analysis seeks to inform short-term cost-effectiveness of prolapse treatment options. Data from the three-way comparison are further used to populate a Markov cohort decision-analytic model, which explores longer-term costs and QALY implications of prolapse treatment. The methods underpinning the model and the longer-term cost-effectiveness results are presented in *Chapter 9*.

EuroQol-5 Dimensions (3-level version), quality-adjusted life-years

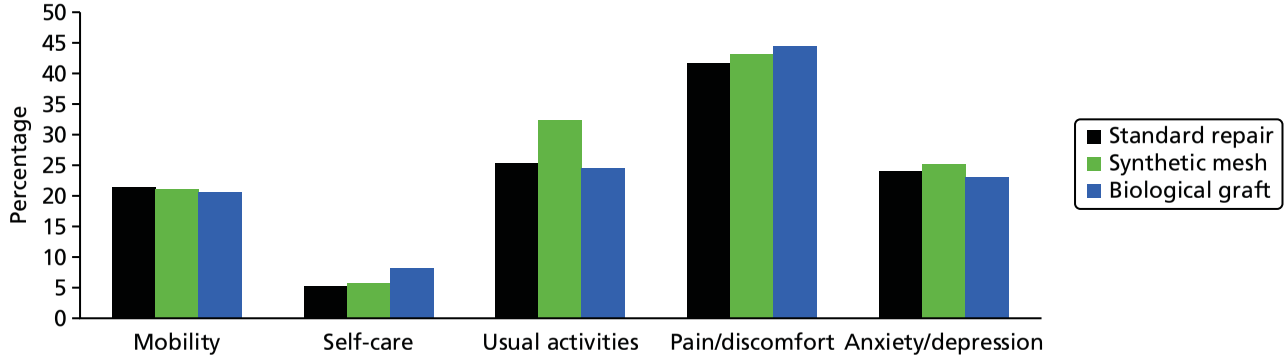
The proportion of women with any health problems reported on the EQ-5D-3L measure of generic QoL is shown in *Figures 5–7*. These figures present the data as reported by women across randomised groups at 6 months, 1 year and 2 years, respectively. The descriptive data in *Figures 5–7* are based on all of the available data recorded. This contrasts with the economic evaluation data in later sections, which are based on complete cost and QALY pairs. The figures illustrate the percentage of women who were having any problems on each of the domains of QoL (i.e. women scoring a '2' or a '3'). In general, a substantial proportion of women appear to have some pain or discomfort, with little difference between 6-month and 1-year follow-up. The fewest problems were experienced in self-care, with only a small proportion of women reporting any problems. A visual inspection of the graphical data does not indicate any substantial differences between the percentage of women reporting problems across the randomised groups in any of the individual dimensions of generic QoL at 6 months or 1- or 2-year time points.

Figures 5–7 indicate the individual aspects of QoL that impact on overall utility for these women. *Table 39* provides descriptive data of mean utility scores (generated using time trade-off tariffs, based on UK general population norms[25]) and QALYs generated by combining utilities with duration (length) of life over follow-up.



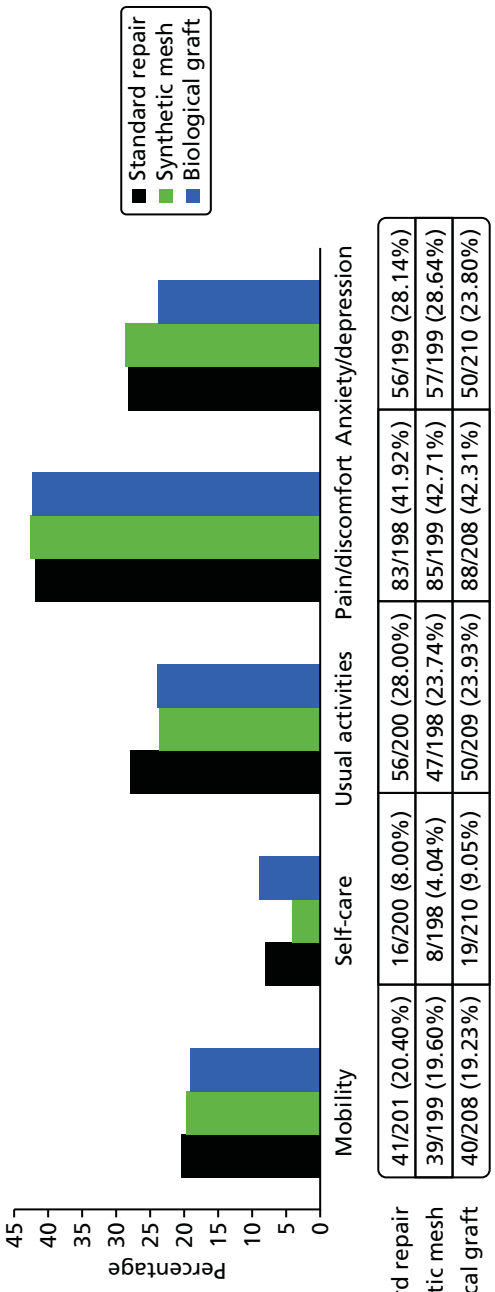
	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Standard repair	42/225 (18.67%)	12/227 (5.29%)	56/227 (24.67%)	89/227 (39.21%)	60/228 (26.31%)
Synthetic mesh	42/222 (18.92%)	12/221 (5.43%)	68/221 (30.77%)	95/222 (42.79%)	65/221 (29.41%)
Biological graft	48/222 (21.62%)	20/221 (9.05%)	70/222 (31.53%)	95/220 (43.18%)	57/220 (25.91%)

FIGURE 5 Proportion of women experiencing any problems on each EQ-5D-3L domain at 6 months. Analysis based on all of the available EQ-5D data points.



	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Standard repair	50/232 (21.55%)	12/231 (5.19%)	59/232 (25.43%)	97/232 (41.81%)	56/232 (24.14%)
Synthetic mesh	48/225 (21.33%)	13/225 (5.78%)	73/226 (32.30%)	97/224 (43.31%)	57/225 (25.34%)
Biological graft	47/228 (20.61%)	19/229 (8.30%)	56/228 (24.57%)	102/229 (44.54%)	53/229 (23.14%)

FIGURE 6 Proportion of women experiencing any problems on each EQ-5D-3L domain at 1 year. Analysis based on all of the available EQ-5D data points.



	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Standard repair	41/201 (20.40%)	16/200 (8.00%)	56/200 (28.00%)	83/198 (41.92%)	56/199 (28.14%)
Synthetic mesh	39/199 (19.60%)	8/198 (4.04%)	47/198 (23.74%)	85/199 (42.71%)	57/199 (28.64%)
Biological graft	40/208 (19.23%)	19/210 (9.05%)	50/209 (23.93%)	88/208 (42.31%)	50/210 (23.80%)

FIGURE 7 Proportion of women experiencing any problems on each EQ-5D-3L domain at 2 years. Analysis based on all of the available EQ-5D data points.

TABLE 39 EuroQol-5 Dimensions (3-level version) at each time point: Primary trial

Treatment group	Standard repair: mean (SD); *n*	Synthetic mesh: mean (SD); *n*	Biological graft: mean (SD); *n*
EQ-5D-3L: baseline	0.722 (0.245); 231	0.711 (0.233); 234	0.697 (0.265); 230
EQ-5D-3L: 6 months	0.810 (0.284); 222	0.816 (0.229); 219	0.798 (0.268); 215
EQ-5D-3L: 12 months	0.816 (0.273); 227	0.827 (0.217); 223	0.809 (0.267); 228
QALYs gained[a] (baseline to 1 year)	*0.792(0.235); 197*	*0.808 (0.174); 196*	*0.778 (0.231); 193*
EQ-5D-3L: 24 months	0.796 (0.293); 196	0.825 (0.230); 198	0.810 (0.270); 207
QALYs[b] (baseline to 2 years)	*1.573 (0.498); 169*	*1.644 (0.302); 171*	*1.579 (0.452); 173*

a QALYs gained are based on an area under the curve analysis, whereas EQ-5D-3L utilities are point estimates at the follow-up time-points.
b QALYs in second year are discounted at a rate of 3.5% per annum.

Results for incremental QALYs gained are presented comparing synthetic mesh/biological graft with standard repair for both raw differences between QALY estimates and also modelled differences. The modelled differences are based on linear regression (OLS) models, with adjustment for baseline covariates, including baseline EQ-5D-3L score, surgeon, age, BMI, concomitant continence procedure at baseline and compartment of prolapse.

Analyses were conducted using heteroscedastic robust SEs. *Table 40* presents the incremental QALYs gained for each group at both 1 year and 2 years, calculated using an area-under-the-curve approach.

There were no statistically significant differences in QALYs between treatment groups over 1 year of follow-up. In terms of covariates included within the analysis model, baseline utility was the only significant predictor of overall QALYs in the model, indicating that QALYs were influenced by baseline EQ-5D-3L score. This is to be expected, given that we use an area-under-the-curve approach to calculate QALYs gained between EQ-5D-3L-reported time points, which are thus influenced by the starting point EQ-5D-3L score. Furthermore, the age of the women was not found to impact on QALY estimates or was the result impacted by type of prolapse (anterior/posterior) or whether or not the woman had a concomitant continence procedure. Overall, there is no evidence of any difference in generic QoL between randomised groups over the first year of follow-up.

TABLE 40 Incremental QALYs (three-arm RCT1A only)

	1-year outcomes			2-year outcomes[b]		
QALYs	Mean (SD); *n*	Raw MD (vs. standard)	Adjusted MD (vs. standard); (95% CI)[a]	Mean (SD); *n*	Raw MD (vs. standard)	Adjusted MD (vs. standard); (95% CI)[a]
Standard repair	0.792 (0.235); 197	–	–	1.573 (0.498); 169	–	–
Synthetic mesh	0.808 (0.174); 196	0.016	0.0109 (–0.021 to 0.043)	1.644 (0.302); 171	0.071	0.071 (–0.004 to 0.145)
Biological graft	0.778 (0.231); 193	–0.014	–0.001 (–0.036 to 0.033)	1.579 (0.452); 173	0.006	0.039 (–0.041 to 0.120)

a Regression analysis based on non-parametric bootstrapped OLS regression, with adjustment for age, BMI, whether or not the surgeon performing the operation was based as a main lead site (Aberdeen, Manchester and Plymouth), concomitant continence procedure, anterior prolapse or baseline utility. Heteroscedastic robust SEs are used.
b QALYs in second year discounted at 3.5% per annum.

There were no significant differences between the groups regarding QALYs gained at 2 years. However, the point estimates of QALYs were higher in both synthetic mesh and the biological graft groups, especially synthetic mesh, with a large proportion of the distribution predicting positive QALY gains for synthetic mesh. Nevertheless, there remains some uncertainty regarding the most beneficial treatment strategy in terms of QALYs gained from the trial-based analysis.

NHS resource use and costs

Costs to health services

Costs include intervention procedure costs, inpatient and follow-up secondary care costs, and costs of primary care services relating to the index prolapse surgery. This may include for example treatment of complications, treatment failure or increased contact with health-care professionals for prolapse-related issues. Similarly to the presentation of QALY data, the descriptive statistics and the regression analyses are based on complete case data for those women randomised across all three groups (i.e. RCT1A). The total NHS costs are calculated by multiplying resource use by the appropriate unit cost estimates outlined in *Table 2* (see *Chapter 2*).

Intervention costs

The total costs to the NHS, based on the microcosting approach using data collected within the trial are presented in *Table 41*. There were no significant differences between groups in terms of staff time and length of hospitalisation costs. This is suggestive of similar operation, equipment and surgical expertise required to perform all types of procedures (whether mesh based or not). Despite substantial variation in costs of length of initial hospitalisation for a prolapse procedure, there was substantial uncertainty and no clear statistical differences between groups.

The intervention costs of synthetic mesh and biological graft repairs were substantially and statistically significantly more expensive than standard midline repairs as a result of the additional cost of materials required to carry out the procedures. There was substantial variation in the price of mesh across different products within similar groups. These analyses make no statements about the effectiveness of one material relative to another, and are based on the assumption that mesh or graft material products within a category are equally effective (i.e. assuming all types of synthetic mesh are equally effective and all types of biological graft are equally effective). The variability in the price of mesh procedures across participating sites, using alternative mesh products is evident through the large SDs for mesh costs presented in *Table 41*.

Health services resource-use costs over trial follow-up

The additional costs of mesh procedures are combined with costs to the health services over the trial follow-up period for each treatment group and are presented in *Table 42*. These include all secondary care (readmissions, reoperations, visits to ward, outpatient consultations) and primary care (e.g. GP, nurse, physiotherapist) contacts with health professionals. We have taken the following approach to presentation of cost data. Each category of cost is presented for full cases within that category (e.g. hospital resource use, primary care costs). These are then summed, along with the intervention cost, for complete cases across all the categories, and presented as the total cost to the health services at 2 years. Data presented in *Table 42* and for the statistical analyses are based on the three-way comparison (i.e. RCT1A).

At 1 year post operation, based on the data available from RCT1A, synthetic mesh and biological graft are both significantly more costly than the standard repair, with biological graft being the most expensive treatment option. Biological graft is significantly more expensive over 2 years of follow-up. There remains some weak evidence ($p < 0.1$) that synthetic mesh is also more costly to the health services over 2 years. These outcomes would be expected, given that the additional cost of mesh is applied to these arms in the intervention costing. It is important to conclude that there is no evidence of differences in costs of follow-up care between any of the trial interventions. Overall, over a 2-year time horizon, including

TABLE 41 Intervention costs

	Standard repair			Synthetic mesh			Biological graft			Incremental analysis	
Intervention cost table	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Synthetic vs. standard (£): MD (95% CI)[a]	Biological vs. standard (£): MD (95% CI)[a]
Mesh cost	0	7	247	137	175	248	288	265	251		
Staff time in theatre	920	428	252	963	373	255	922	361	255		
Cost of drugs in theatre	24	8	252	24	8	255	25	7	255		
Cost of catheterisation	5	2	252	6	2	255	6	2	255		
Cost of vaginal packing	4	2	252	4	2	255	4	2	255		
Theatre overheads	465	217	252	491	184	255	473	182	255		
Subtotal: theatre costs	*1420*	*649*	*247*	*1627*	*591*	*248*	*1718*	*595*	*251*		
Costs from theatre – discharge	1411	919	247	1501	891	248	1540	1083	251		
Total intervention costs	***2831***	***1151***	***247***	***3128***	***1042***	***248***	***3258***	***1279***	***251***	***251 (46 to 455)***	***499 (265 to 732)***

a Incremental analysis is based on data from RCT1A only and adjusted for minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score The model applied to all of the data reported is the OLS linear model.

TABLE 42 Health-care resource use and costs (NHS perspective)

	Resource use			Costs				
							Incremental analysis of costs[a]	
NHS resource use and costs	Standard repair	Synthetic mesh	Biological graft	Standard repair: mean (SD); *N*	Synthetic mesh: mean (SD); *N*	Biological graft: mean (SD); *N*	Synthetic vs. standard	Biological vs. standard
Total intervention costs				2831 (1151); 247	3128 (1042); 248	3258 (1279); 251	251 (46 to 455)	499 (265 to 732)
1-year data								
Hospital resource use (0–6 months)								
New prolapse procedure; *n/N* (%)	1/232 (0.4%)	3/224 (1.3%)	2/228 (0.9%)					
New incontinence procedure; *n/N* (%)	1/232 (0.4%)	0/224 (0.0%)	0/228 (0.0%)					
Other related readmissions; *n/N* (%)	6/232 (2.6%)	12/224 (5.4%)	7/228 (3.1%)					
Further prolapse-related surgery within 6 months; n/N (%)	*8/232 (3.9%)*	*15/224 (7.1%)*	*9/228 (4.4%)*	*47 (259); 232*	*92 (368); 224*	*54 (288); 228*		
Outpatient visits; *n/N* (%)	9/232 (3.9%)	13/224 (5.8%)	21/228 (9.2%)	5 (26); 232	8 (31); 224	12 (39); 228		
Subtotal (hospital use 0–6 months)				*52 (260); 232*	*100 (368); 224*	*66 (288); 228*	*43 (–24 to 112)*	*–8 (–60 to 44)*
Hospital resource use (6–12 months)								
New prolapse procedure; *n/N* (%)	5/233 (2.1%)	8/226 (3.5%)	10/230 (4.3%)	50 (339); 233	83 (432); 226	101 (476); 230		
New incontinence procedure; *n/N* (%)	2/233 (0.9%)	1/226 (0.4%)	3/230 (0.9%)	12 (127); 233	6 (91); 226	18 (156); 230		
Other related readmissions; *n/N* (%)	4/233 (1.7%)	11/226 (4.9%)	5/230 (2.2%)	17 (134); 233	52 (233); 226	19 (131); 230		
Outpatient visits: mean (SD)	0.38 (0.72)	0.62 (1.02)	0.49 (0.80)	45 (78); 233	68 (100); 226	56 (84); 230		
Subtotal (hospital use 6–12 months)				*124 (404); 232*	*208 (513); 226*	*194 (546); 230*	*86 (–7 to 179)*	*54 (–42 to 150)*

continued

TABLE 42 Health-care resource use and costs (NHS perspective) (*continued*)

	Resource use			Costs				
							Incremental analysis of costs[a]	
NHS resource use and costs	Standard repair	Synthetic mesh	Biological graft	Standard repair: mean (SD); *N*	Synthetic mesh: mean (SD); *N*	Biological graft: mean (SD); *N*	Synthetic vs. standard	Biological vs. standard
Other consultations (0–12 months)								
Physiotherapy: mean (SD)	0.21 (0.94)	0.23 (1.02)	0.17 (0.78)	5 (23); 232	6 (24); 226	4 (19); 230		
GP nurse: mean (SD)	0.04 (0.23)	0.17 (0.74)	0.10 (0.80)	1 (3); 233	2 (10); 226	1 (11); 230		
GP doctor: mean (SD)	0.43 (1.07)	0.68 (1.56)	0.51 (1.16)	20 (49); 233	31 (72); 226	23 (53); 229		
Other: mean (SD)	0.04 (0.27)	0.03 (0.20)	0.04 (0.33)	3 (29); 233	1 (8); 225	1 (7); 229		
Subtotal (other consultations 0–12 months)				*28 (70); 232*	*40 (86); 225*	*30 (62); 228*	*12 (–4 to 29)*	*1 (–12 to 15)*
Other treatments (0–12 months)								
Shelf pessary; *n/N* (%)	4/233 (1.7%)	3/226 (1.3%)	3/230 (1.3%)	1 (8); 233	1 (7); 226	1 (7); 230		
Ring pessary; *n/N* (%)	5/233 (2.2%)	6/226 (2.7%)	5/230 (2.2%)	1 (6); 233	1 (6); 226	1 (6); 230		
Incontinence drugs; *n/N* (%)	14/233 (6.0%)	21/226 (9.3%)	15/230 (6.5%)	3 (8); 233	4 (10); 226	3 (8); 230		
Oestrogen; *n/N* (%)	34/233 (14.6%)	46/226 (20.4%)	39/230 (17.0%)	3 (7); 233	4 (8); 226	3 (7); 230		
Intermittent catheters; *n/N* (%)	3/232 (1.3%)	4/224 (1.8%)	6/230 (2.6%)	23 (205); 233	32 (240); 226	47 (290); 230		
Permanent catheter; *n/N* (%)	1/232 (0.4%)	1/224 (0.5%)	0/230 (0.0%)	2 (26); 233	2 (26); 226	0 (0); 230		
Absorbent pads; *n/N* (%)	70/233 (30.0%)	67/226 (29.7%)	60/230 (26.1%)	217 (367); 233	225 (459); 226	166 (302); 230		
Other drug treatments; *n/N* (%)	15/233 (6.4%)	10/226 (4.4%)	9/230 (3.9%)	3 (14); 233	9 (94); 226	1 (5); 230		
Subtotal (other treatments 0–12 months)				*253 (412); 233*	*278 (546); 226*	*223 (403); 230*	*–21 (–120 to 77)*	*–47 (–132 to 38)*
Total 1-year follow-up costs				***461 (706); 222***	***622 (967); 211***	***499 (778); 219***	***112 (–64 to 288)***	***–4 (–160 to 151)***
Total health services costs (1 year)				***3240 (1304); 222***	***3702 (1358); 211***	***3800 (1495); 219***	***438 (168 to 708)***	***611 (332 to 891)***

NHS resource use and costs	Resource use			Costs[b]				
							Incremental analysis of costs	
	Standard repair	Standard repair	Standard repair	Standard repair: mean (SD); *N*	Synthetic mesh: mean (SD); *N*	Biological graft: mean (SD); *N*	Synthetic vs. standard	Biological vs. standard
2-year data								
Hospital resource use (12–24 months)								
New prolapse procedure; *n/N* (%)	11/202 (5.4%)	9/201 (4.5%)	9/209 (4.3%)	123 (512); 202	101 (467); 201	97 (458); 209		
New incontinence procedure; *n/N* (%)	4/202 (2.0%)	1/201 (0.5%)	4/209 (1.9%)	26 (185); 202	7 (94); 201	25 (182); 209		
Other related readmissions; *n/N* (%)	2/202 (1.0%)	10/201 (5.0%)	2/209 (1.0%)	10 (98); 202	52 (232); 201	9 (97); 209		
Outpatient visits: mean (SD)	0.19 (0.55)	0.23 (0.57)	0.28 (0.66)	18 (50); 202	22 (55); 200	26 (60); 209		
Subtotal (hospital resource use 12–24 months)	–	–	–	*177 (603); 202*	*182 (554); 200*	*158 (523); 209*	*–33 (–156 to 90)*	*–22 (–149 to 106)*
Other consultations (12–24 months)								
Physiotherapy: mean (SD)	0.19 (1.06)	0.25 (1.03)	0.22 (1.00)	4 (25); 202	6 (24); 202	5 (23); 210		
GP nurse: mean (SD)	0.03 (0.23)	0.03 (0.27)	0.03 (0.22)	0 (3); 202	0 (4); 202	0 (3); 210		
GP doctor: mean (SD)	0.32 (2.17)	0.40 (1.17)	0.19 (0.63)	14 (97); 202	18 (52); 202	9 (28); 209		
Other: mean (SD)	0.04 (0.34)	0.08 (0.67)	0.03 (0.31)	0 (3); 200	0 (4); 201	0 (6); 209		
Subtotal other consultations (12–24 months)				*20 (102); 200*	*24 (61); 201*	*15 (43); 208*	*6 (–14 to 26)*	*–7 (–26 to 11)*

continued

TABLE 42 Health-care resource use and costs (NHS perspective) (*continued*)

	Resource use			Costs[b]				
							Incremental analysis of costs	
NHS resource use and costs	Standard repair	Standard repair	Standard repair	Standard repair: mean (SD); *N*	Synthetic mesh: mean (SD); *N*	Biological graft: mean (SD); *N*	Synthetic vs. standard	Biological vs. standard
Other treatments (12–24 months)								
Shelf pessary	5/202 (2.5%)	2/202 (1.0%)	5/210 (2.4%)	2 (10); 202	1 (6); 201	1 (10); 209		
Ring pessary	6/202 (3.0%)	5/202 (2.5%)	9/210 (4.3%)	1 (7); 202	1 (6); 201	2 (8); 209		
Incontinence drugs	16/202 (7.9%)	16/202 (7.9%)	18/210 (8.6%)	3 (7); 202	3 (9); 201	3 (7); 209		
Oestrogen	27/202 (13.4%)	35/202 (17.3%)	32/210 (15.2%)	5 (9); 204	6 (10); 208	5 (9); 216		
Intermittent catheters	4/201 (2.0%)	3/201 (1.5%)	4/210 (1.9%)	35 (245); 202	26 (213); 201	33 (240); 210		
Permanent catheter	0/202 (0.00%)	0/201 (0.00%)	0/210 (0.00%)	0 (0); 202	0 (0); 201	0 (0); 209		
Absorbent pads	57/201 (28.4%)	52/201 (25.9%)	57/209 (27.3%)	247 (537); 202	191 (421); 202	195 (373); 210		
Other drug treatments	10/202 (5.0%)	8/201 (4.0%)	6/210 (2.9%)	2 (12); 202	15 (140); 201	0 (2); 210		
Subtotal, other treatments (12–24 months)				*293 (629); 202*	*241 (500); 201*	*229 (433); 209*	*–86 (–213 to 42)*	*–80 (–200 to 40)*
Total 2-year follow-up costs (12–24 months)				***459 (972); 200***	***439 (841); 199***	***393 (692); 207***	***–91 (–294 to 112)***	***–84 (–275 to 107)***
Total health services costs (2 years)				***3685 (1769); 194***	***4112 (1756); 184***	***4194 (1743); 196***	***363 (–32 to 758)***	***565(180 to 950)***

a Incremental analysis is based on data from RCT1A only and adjusted for minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score.
b Costs in second year discounted at a rate of 3.5% per annum.

intervention and follow-up health services costs, synthetic mesh is, on average, £363 more costly than standard repair (95% CI –£32 to £758) based on costs discounted at a rate of 3.5% per annum, applied to the second year of follow-up. Biological graft is estimated to be £565 more expensive than standard repair (95% CI £180 to £950). It is clear that from the perspective of NHS payers that mesh products, and in particular biological graft prolapse repairs, present significant cost outlay for provision of care.

Base-case cost-effectiveness results (NHS perspective)

Given that there are no substantial counteracting cost savings of follow-up care over the shorter-term time horizon, it is necessary to compare the additional costs of mesh repairs with any potential gains in QoL. The base-case economic (cost–utility) analysis is presented according to the regression models outlined for costs and QALYs in *Chapter 2*. The base-case economic analysis is presented for complete case data of cost and QALY pairs, ensuring that the joint distribution of costs and effects is not broken. As with the data presented in previous tables, all analyses are for women randomised to the three-way (RCT1A) trial comparison.

One-year cost-effectiveness results

Table 43 presents the main results of the economic analysis from a NHS perspective over a 1-year time horizon. Based on these data, at 1-year follow-up, biological graft is not a cost-effective alternative to either standard repair or synthetic mesh, as it is more costly and generates fewer QALYs. Furthermore, at 1-year follow-up, it is unlikely that synthetic mesh would offer a cost-effective treatment option, with an ICER of £35,750 per QALY gained, it is above the £20,000–30,000 threshold value of cost-effectiveness commonly accepted by UK decision-makers. *Figure 8* illustrates the scatterplot of incremental costs and incremental QALYs for this analysis, showing substantial uncertainty in QALYs gained, but definitively showing that in nearly all of the simulations both mesh procedures are more expensive than standard repair. The CEAC in *Figure 9* shows that at 1-year follow-up, based on the NMB, there is substantial uncertainty regarding the most cost-effective treatment strategy. On the balance of probabilities, data from the CEACs indicate that standard repair has a slightly higher probability of being the most cost-effective treatment strategy than alternative options up to a WTP of approximately £40,000 per QALY gained. Considering that decision-makers may be willing to pay £30,000 for a QALY gained, there is a 57% chance that standard repair and 40% chance that synthetic mesh are the most cost-effective treatments. There is little chance biological graft would be cost-effective. However, as the threshold of WTP for a QALY increases, the probability that synthetic mesh becomes cost-effective increases. Overall, the data do not allow one to draw clear conclusions on cost-effectiveness over a 1-year follow-up.

Two-year cost-effectiveness results

The results of the cost-effectiveness analysis over 2 years is presented in *Table 44*. Two analyses are undertaken: the base-case analysis presents complete case data, and the secondary analysis presents the results from an imputed data set. In all cases, costs and outcomes for the second year of follow-up are discounted at a rate of 3.5% in accordance with economic evaluation best practice guidelines.

Complete case analysis

The results of the complete case analysis show that synthetic mesh provides greater QALYs than standard repair, for an analysis in which complete case cost and QALY pairs are considered. This leads to a favourable point estimate of the ICER for synthetic mesh compared with standard repair of £4493 per QALY gained, falling well below a threshold value of WTP for a QALY gained. Biological graft repair is not cost-effective. Although its ICER compared with standard repair is just over £13,000 per QALY, it is more costly and less effective than synthetic mesh. Biological graft is therefore dominated by synthetic mesh

TABLE 43 Base-case cost-effectiveness results: complete case data (1 year)

Treatment	Costs: mean (SD)	Incremental costs (vs. standard)[a]	QALYs: mean (SD)	Incremental QALYs (vs. standard)[a]	Incremental cost (£) per QALY gained (vs. standard)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[b]				
						£0	£10,000	£20,000	£30,000	£50,000
Standard repair ($n = 195$)	3216 (1301)	–	0.790 (0.236)	–	–	1.00	0.91	0.70	0.57	0.43
Synthetic mesh ($n = 195$)	3698 (1387)	429 (161 to 697)	0.808 (0.174)	0.012 (–0.021 to 0.044)	*35,750*	0.00	0.09	0.29	0.40	0.50
Biological graft ($n = 191$)	3823 (1500)	600 (316 to 885)	0.781 (0.231)	–0.001 (–0.038 to 0.036)	*Dominated*	0.00	0.00	0.02	0.04	0.07

a Incremental analysis is based on data from RCT1A only and adjusted for minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score. The model applied to all of the data reported is the OLS linear model.

b As a result of rounding, values in probability may add to 0.99 or 1.01; based on complete case data at 1-year follow-up time point.

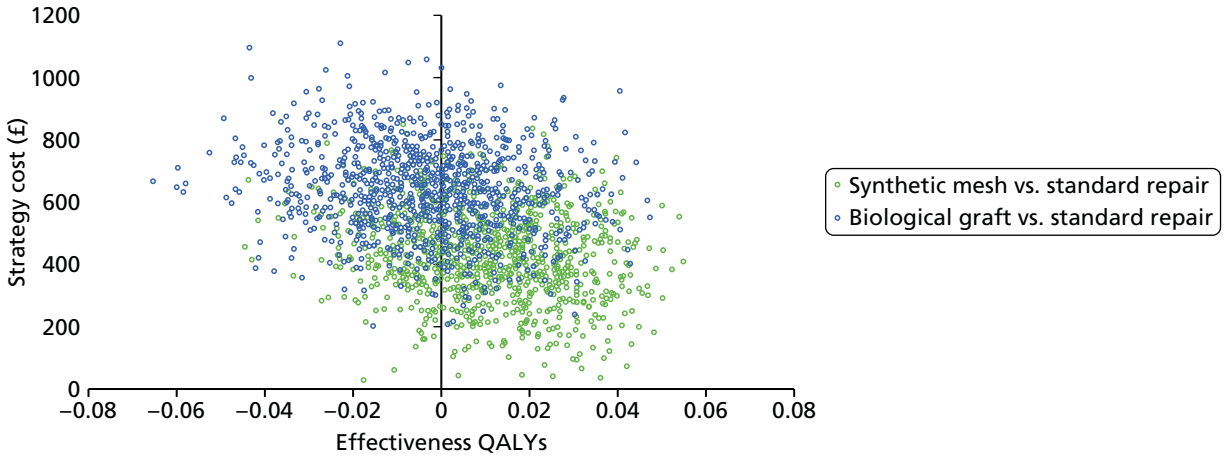


FIGURE 8 Scatterplot of incremental costs and QALYs for mesh treatments compared with standard repair: 1-year follow-up data.

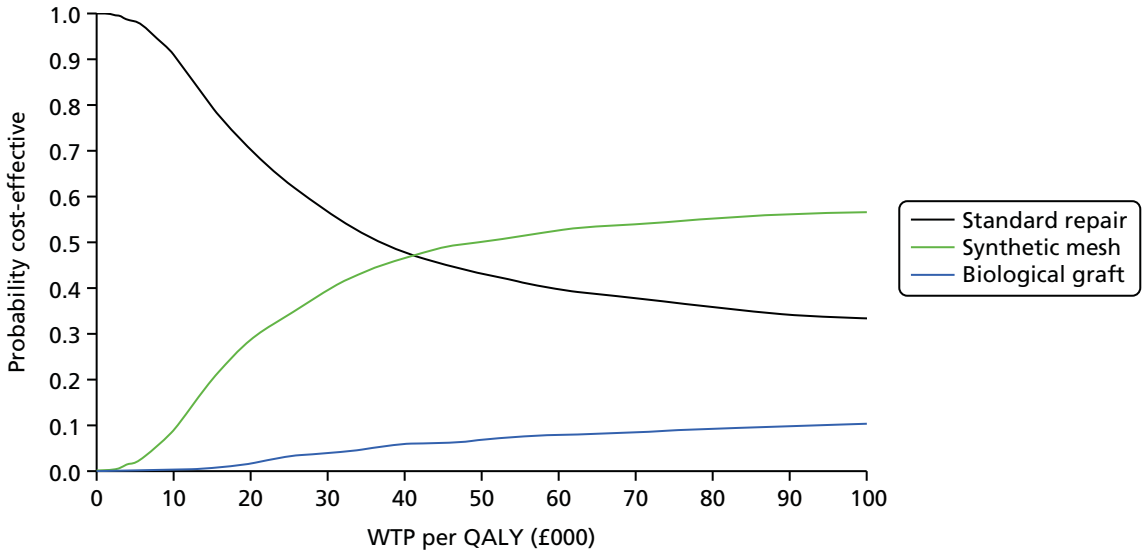


FIGURE 9 Cost-effectiveness acceptability curves: 1-year follow-up data.

and, based on current data, is not a cost-effective use of resources. However, this estimate should be interpreted in light of the considerable uncertainty surrounding it. *Figures 10* and *11* present the scatterplot and CEACs, respectively, for the 2-year outcomes. Despite the favourable point estimate of the ICER for synthetic mesh repair, there remains some uncertainty, with an 84% probability, that synthetic mesh is the most cost-effective treatment strategy. The probability of biological repair being the preferred treatment option is substantially lower, never reaching a probability of cost-effectiveness of > 13% at threshold values of up to £50,000 per QALY gained.

Based on the complete case analysis of 2-year cost-effectiveness outcomes, there is no definitive evidence regarding the most cost-effective treatment strategy, although synthetic mesh may offer a cost-effective alternative to standard repair, depending on the threshold of WTP for a QALY gained adopted by a decision-maker. The higher the threshold value, the more likely it is that synthetic mesh would be considered a cost-effective use of NHS resources.

TABLE 44 Two-year cost-effectiveness results

Treatment	Costs: mean (SD)	Incremental costs[a,b] (vs. standard)	QALYs: mean (SD)	Incremental QALYs[a,b] (vs. standard)	Incremental cost (£) per QALY gained (vs. standard)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[c]				
						£0	£10k	£20k	£30k	£50k
Complete case analysis										
Standard repair ($n = 165$)	3664 (1777)		1.569 (0.502)		–	0.93	0.19	0.08	0.05	0.03
Synthetic mesh ($n = 168$)	4081 (1762)	337 (–73 to 747)	1.643 (0.304)	0.075 (0.000 to 0.150)	*4493*	0.06	0.75	0.83	0.84	0.84
Biological graft ($n = 170$)	4165 (1691)	555 (156 to 954)	1.582 (0.455)	0.041 (–0.042 to 0.124	*13,537*	0.00	0.07	0.10	0.12	0.13
Imputed data set analysis										
Standard repair ($n = 647$)	3570 (468)		1.559 (0.297)			0.93	0.69	0.57	0.52	0.47
Synthetic mesh ($n = 647$)	3889 (468)	319 (–56 to 694)	1.555 (0.297)	–0.003 (–0.068 to 0.063)	*Dominated*	0.07	0.22	0.28	0.29	0.30
Biological graft ($n = 647$)	4098 (468)	527 (161 to 893)	1.554 (0.297)	–0.004 (–0.073 to 0.065)	*Dominated*	0.00	0.09	0.16	0.20	0.23

a Results based on costs and QALYs discounted by 3.5% per annum in the second year.
b Incremental analysis is based on data from RCT1A only and adjusted for minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score. The model applied to all of the data reported is the OLS linear model.
c As a result of rounding, values in probability may add to 0.99 or 1.01.

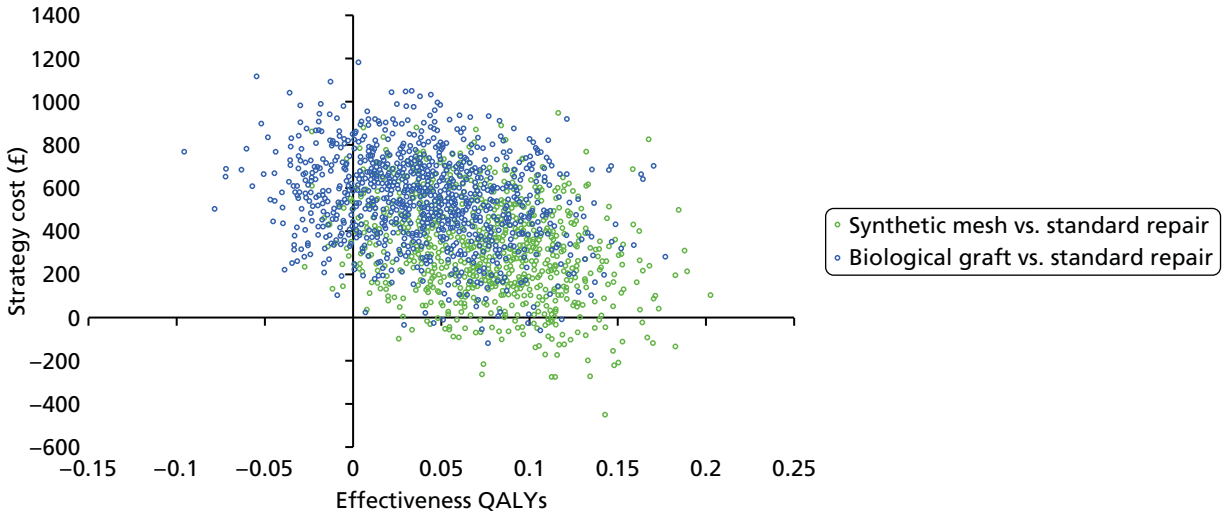


FIGURE 10 Scatterplot of incremental costs and QALYs for mesh treatments compared with standard repair: complete case analysis, 2-year follow-up data.

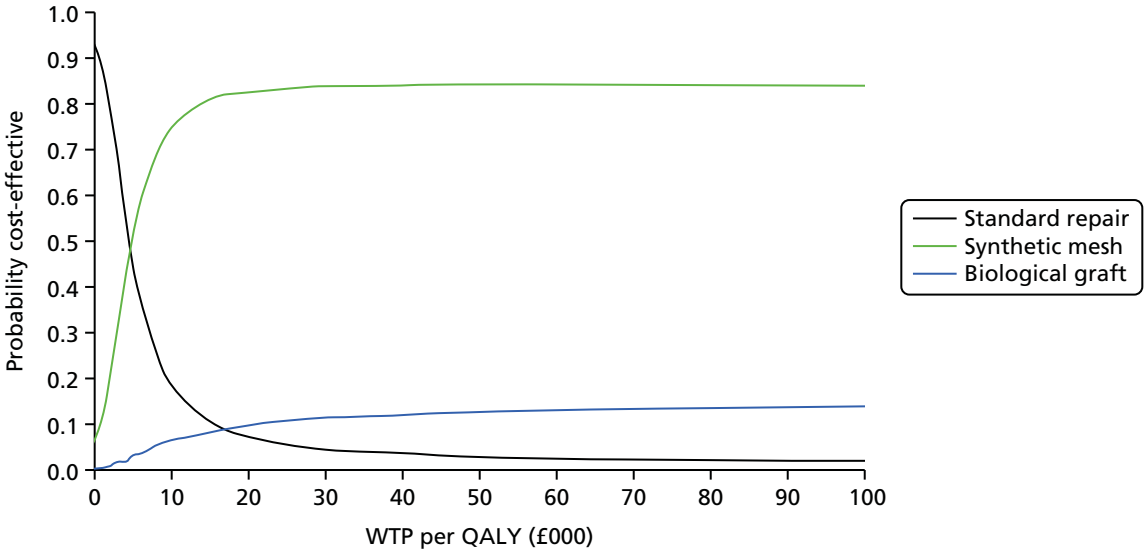


FIGURE 11 Cost-effectiveness acceptability curves: complete case analysis, 2-year follow-up data.

Missing data

The complete case analysis results showed potential improvements in QALY gains for synthetic mesh at 2 years. However, the analysis of complete case QALY data ignored some important missing data information, with a substantial proportion of participants missing complete QALY data at each time point up to 2 years. Data completeness for QALYs at 2 years was evenly distributed across the different arms of the trials with missing data 83 of 252 (33%), 84 of 255 (33%) and 82 of 255 (32%) for standard repair, synthetic mesh and biological graft, respectively. Further analysis shows that participants suffering from failures or complications tended to report less-complete EQ-5D-3L data than those not experiencing such effects. For example, missing data for 2-year QALYs for those with severe complications was between 40% and 45% across the randomised groups. Furthermore, we investigated the mechanism of missingness of data by exploring the impact of baseline covariates on missing data. Missing data were found to differ

significantly between age groups, with older women reporting more complete data. We therefore excluded the assumption that missing QALY data were missing at random. This finding, together with the extent of missingness, particularly among respondents experiencing negative health effects, is suggestive that the complete case analyses may overestimate true QALYs for women who are experiencing prolapse. Multiple imputed data analysis explores the impact of missing data on results. The analysis reported in the lower section of *Table 44* imputes data based on predictive mean matching for QALYs and standard multivariate regression models for costs. Estimates of incremental costs were not found to impact on overall results. It can be seen from the results that there remains substantial uncertainty regarding the most cost-effective treatment strategy, but, based on data imputation, the potential QALY gains for mesh in the complete case analysis have been removed and all of the strategies generate broadly similar outcomes. Given that there remain no QALY differences between mesh and standard repairs in the imputed data set, mesh is no longer a viable alternative from a cost-effectiveness point of view, and both meshes are dominated by the standard repair approach. As with all of the other analyses, however, there remains substantial uncertainty surrounding the point estimates of cost-effectiveness, with a probability of cost-effectiveness of standard repair (52%), synthetic mesh (29%) and biological repair (20%) at a WTP of £30,000 per QALY gained in the imputed data set compared with 5%, 84% and 12%, respectively, in the base-case analysis.

Considering the two analyses presented for complete case and imputed data sets, there is some uncertainty regarding cost-effectiveness from the within-trial analyses. Although the within-trial analysis is informative regarding short-term cost-effectiveness, and determining drivers of uncertainty, it is likely that the true cost-effectiveness of mesh materials will not be determined by such a short time horizon, which may be insufficient to capture longer-term risk of recurrence and any associated complications. It is therefore necessary to consider longer-term outcomes of cost-effectiveness. This will be achieved by continuing the PROSPECT follow-up to a minimum of 6 years, and through the development of a decision-analytic model presented in *Chapter 9*. The decision model will make initial projections of longer-term cost-effectiveness, which will be validated using the longer-term trial follow-up once the data become available.

Costs directly incurred by participants and indirect costs

A further analysis was conducted incorporating both participant and indirect costs into the analysis over the 2-year study follow-up.

Table 45 reports mean costs (from a wider economic perspective) of attending primary care, outpatient appointments and inpatient admissions, respectively. We have taken the following approach to presentation of data in *Table 45*. Each category of cost is presented for full cases within that category (e.g. time off work due to prolapse symptoms). These are then summed together, across all the categories for all available cost data for participant and companion time and travel costs, and presented as the total participant cost at 2 years. Complete case data for participant total cost and NHS total cost are then added together to generate a wider economic cost.

The analysis includes participant-incurred costs for attending their PROSPECT surgery. As women with prolapse symptoms attended a large number of consultations and appointments with the health services, the personal and economic cost was also substantial. However, there were no differences across randomised groups, and it is important to note large SDs, which indicate great uncertainty in participant time and travel costs across the groups.

Furthermore, a small proportion of women incurred direct private health-care costs or self-purchased medication. However, the majority did not and, as with the analyses above, there were no differences across groups.

TABLE 45 Participant, companion and indirect costs

	Standard repair			Synthetic mesh			Biological graft			Incremental analysis[a]	
Costs	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Synthetic vs. standard: MD (95% CI)	Biological vs. standard: MD (95% CI)
Time off work due to prolapse problems	1376	4945	236	1207	3475	231	1310	3800	235	20 (–836 to 877)	74 (–769 to 917)
Participant and companion time and travel costs (primary care appointments)	27	168	184	26	63	179	17	51	175	0 (–32 to 32)	–11 (–41 to 20)
Participant and companion time and travel costs (outpatient appointments)	27	53	160	36	61	160	73	281	157	5 (–9 to 18)	56 (–10 to 123)
Participant and companion time and travel costs (inpatient appointments)	266	156	247	262	145	248	263	165	251	–12 (–43 to 19)	–5 (–37 to 28)
Self-purchased health care and medication	3	30	235	4	26	228	16	165	234	0 (–7 to 7)	16 (–10 to 42)
Total indirect and participant costs	*1621*	*4891*	*247*	*1432*	*3417*	*248*	*1562*	*3795*	*251*	*–18 (–853 to 817)*	*70 (–749 to 890)*
Total NHS cost (2 years)	*3685*	*1769*	*194*	*4111*	*1756*	*184*	*4194*	*1743*	*196*	*337 (–73 to 747)*	*555 (156 to 954)*
Overall total NHS, participant and indirect costs	*5431*	*5795*	*194*	*5685*	*4516*	*184*	*5897*	*4582*	*196*	*143 (–1034 to 1319)*	*416 (–715 to 1547)*

a Incremental analysis is based on data from RCT1A only and adjusted for minimisation covariates (age group, type of prolapse, concomitant continence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score. The model applied to all of the data reported is the OLS linear model.

Mean indirect costs of sick leave taken by participants over 2 years for reasons related to prolapse symptoms were £1376, £1207 and £1310 per woman for standard repair, synthetic mesh and biological graft, respectively. This large value reflects the fact that prolapse symptoms have a substantial impact on everyday life for women in terms of financial consequences. However, there were no differences across the randomised groups in terms of time taken as sick leave in relation to prolapse problems and symptoms. The wider economic impact is likely to be greater still if one were to consider the lost productivity of days spent at work, where bothersome symptoms interfered with women's normal work activities but may not necessarily have required sick leave. Therefore, the estimates of true economic cost are likely to be underestimated.

Combining all of the costs of sick leave, opportunity costs of time for participants and companions to attend appointments, travel costs to attend appointments and total costs to the NHS, we can estimate a wider overall economic cost to society. This is limited, of course, to the costs considered, and the true economic costs may be much higher. Nonetheless, the analysis gives an overall impression of the most immediate wider economic costs associated with prolapse surgery and the alternative treatment options considered in the PROSPECT Study. Total economic costs were estimated as £5431, £5685 and £5897 for standard repair, synthetic mesh and biological graft, respectively. By incorporating indirect costs and economic productivity losses of time off work, it is evident that there are substantial costs to prolapse beyond the health sector with substantial impact on prolapse patients, their families and the wider economy. However, incorporating these estimates into the overall analysis greatly increases overall uncertainty, as is evident from the costs presented in *Table 46*, with large SDs surrounding overall economic costs.

Combining the indirect and participant costs with the total NHS costs does not have any substantial impact on overall findings, except to increase the uncertainty surrounding the preferred treatment option. Although the initial point estimates of incremental costs and incremental QALYs tend to favour mesh, with, on average, cost savings and QALY gains, these are meaningless unless considered in the light of the uncertainty surrounding the data. To further explore and illustrate the associated uncertainty, a scatterplot of incremental costs and effectiveness for synthetic mesh and biological graft (compared with standard repair), as well as a CEAC derived from the results of 1000 bootstrapped replicates of mean costs and QALYs are presented. *Figures 12* and *13* illustrate that the probability of standard repair, synthetic mesh or biological graft being the most cost-effective treatment strategy at a threshold value of WTP for a QALY gained of £30,000 are 4%, 84% or 11%, respectively.

The uncertainty surrounding both the NHS- and participant-incurred costs as well as uncertain QALY gains means that there is no clearly definitive cost-effectiveness strategy, even when a wider perspective of economic costs is considered.

Deterministic sensitivity analyses

As demonstrated in the CEACs and scatterplots presented, there is substantial uncertainty driven by data variability in our analysis. Although the complete case analysis indicates that synthetic mesh may be cost-effective with approximately 80% probability at a threshold value of WTP for a QALY gain of £30,000, there remains some uncertainty, particularly in relation to missing data, with no definitively cost-effective strategy emerging. Furthermore, although CEACs and scatterplots based on bootstrapped iterations are important in presenting sampling uncertainty, they do not consider the impact of methodological assumptions, such as the discount rate or the choice of comparison used in the analysis.

A number of sensitivity analyses were carried out, as described in *Chapter 2*, to assess the uncertainty in our results to these data choices and assumptions, particularly around missing data for cost and QALY outcomes. The results of all deterministic sensitivity analyses undertaken are presented in *Table 47*.

TABLE 46 Base-case cost-effectiveness results (incorporating a wider economic perspective)

Treatment	Costs: mean (SD)[a]	Incremental costs (vs. standard)[b]	QALYs: mean (SD)[a]	Incremental QALYs (vs. standard)[b]	Incremental cost (£) per QALY gained (vs. standard)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[c]				
						£0	£10,000	£20,000	£30,000	£50,000
Standard repair ($n = 165$)	5479 (6026)	–	1.569 (0.502)		–	0.43	0.16	0.07	0.04	0.03
Synthetic mesh ($n = 168$)	5740 (4657)	–26 (–1302 to 1250)	1.643 (0.304)	0.075 (0.000 to 0.150)	*Dominant*	0.45	0.74	0.82	0.84	0.85
Biological graft ($n = 170$)	5813 (4199)	306 (–909 to 1521)	1.582 (0.455)	0.041 (–0.042 to 0.124)	*7463*	0.12	0.10	0.11	0.11	0.13

a Results based on costs and QALYs discounted by 3.5% per annum in the second year.
b Incremental analysis is based on data from RCT1A only and adjusted for baseline covariates. The model applied to all of the data reported is the OLS linear model.
c As a result of rounding, values in probability may add to 0.99 or 1.01.

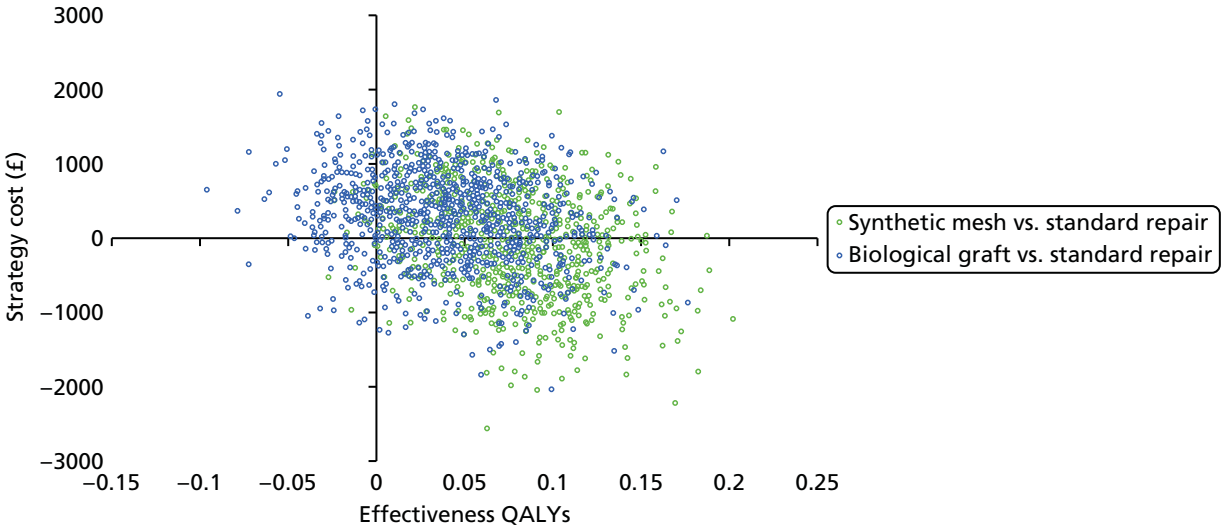


FIGURE 12 Scatterplot of incremental costs and QALYs for mesh treatments vs. standard repair: 2-year follow-up, wider economic perspective.

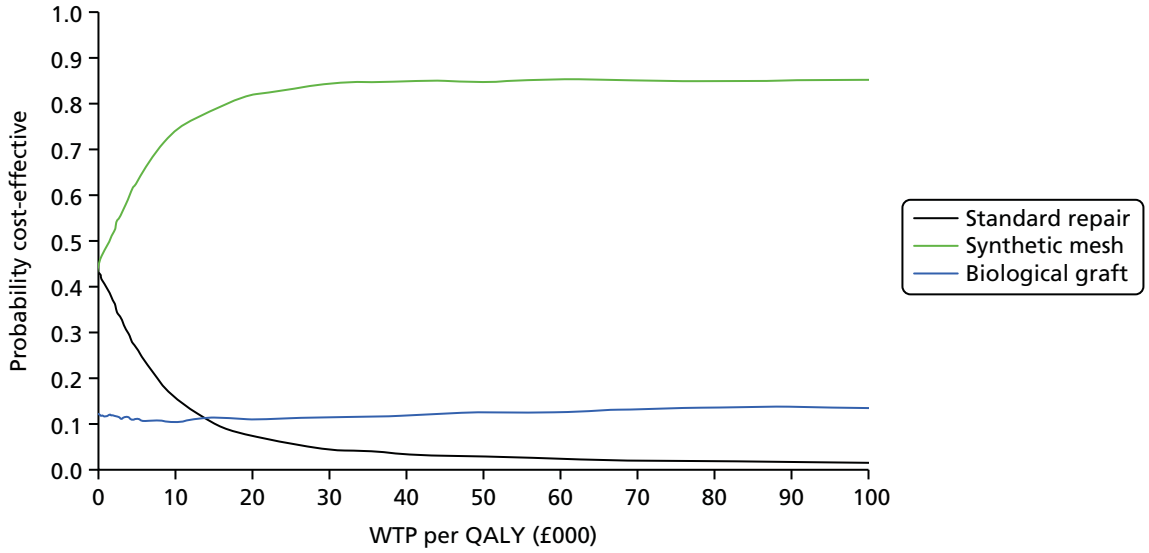


FIGURE 13 Cost-effectiveness acceptability curves: 2-year follow-up, wider economic perspective.

The data on the right-hand side of the table present the probability of cost-effectiveness of each strategy for each analysis undertaken, based on the net benefit statistic, for a £30,000 ceiling ratio of a decision-maker's WTP for a QALY gained. All deterministic sensitivity analyses were carried out on the complete case data set.

Table 47 indicates that for the majority of scenario analyses undertaken, the conclusions remain unchanged, with substantial uncertainty regarding the most cost-effective treatment option. Including an analysis of all women in the Primary trial (i.e. RCT1A, RCT1B and RCT1C) gives broadly similar conclusions. Point estimates of the ICER increase but remain well below £20,000 for the comparison of synthetic mesh with standard repair. The ICER for the comparison of biological graft with standard repair falls. However, in terms of uncertainty, the probability that synthetic mesh is a cost-effective use of resources is lower for the analysis of all women (51%) than the base case (84%) at a £30,000 threshold value of WTP for a QALY gained. It is

TABLE 47 Deterministic sensitivity analyses undertaken for trial-based cost-effectiveness analysis

Analysis	Costs (£)			QALYs			Incremental cost (£)		Incremental QALYs		ICER (£/QALY)		P(CE) @WTP = £30,000/QALY gain[a]		
	Standard repair	Synthetic mesh	Biological graft	Standard repair	Synthetic mesh	Biological graft	Synthetic mesh vs. standard repair	Biological graft vs. standard repair	Synthetic mesh vs. standard repair	Biological graft vs. standard repair	Synthetic mesh vs. standard repair	Biological graft vs. standard repair	Standard repair	Synthetic mesh	Biological graft
Base-case analysis[b]	3664	4081	4165	1.569	1.643	1.582	337 (–73 to 747)	555 (156 to 954)	0.075 (–0 to 0.150)	0.041 (–0.042 to 0.124)	4493	13,537	0.05	0.84	0.12
Costs and QALYs undiscounted[b]	3680	4096	4178	1.596	1.672	1.610	335 (–81 to 751)	553 (149 to 957)	0.077 (0.000 to 0.153)	0.042 (–0.042 to 0.127)	4351	13,167	0.05	0.84	0.12
Costs and QALYs discounted at 6% per annum[b]	3654	4071	4156	1.550	1.624	1.563	339 (–67 to 745)	556 (160 to 953)	0.074 (0.000 to 0.148)	0.040 (–0.041 to 0.122)	4451	13,900	0.05	0.84	0.11
Gamma regression models of cost, with log link[b]	3640	3978	4166	1.569	1.643	1.582	338 (–84 to 760)	526 (123 to 928)	0.075 (–0 to 0.151)	0.041 (–0.043 to 0.125)	4507	12,829	0.03	0.84	0.13
Data from all Primary trial women[c]	3654	4029	4246	1.592	1.641	1.624	483 (214 to 751)	541 (253 to 828)	0.054 (0.004 to 0.104)	0.056 (–0.003 to 0.115)	8944	9661	0.02	0.51	0.47

a 'P(CE) @WTP = £30,000/QALY gain' represents the probability that each intervention is cost-effective, based on the net benefit statistic, if a decision-maker were willing to pay £30,000 for one QALY gained.
b Incremental analysis is based on data from RCT1A only and adjusted for baseline covariates. The model applied to all of the data reported is the OLS linear model.
c For complete case analysis of all Primary trial women, numbers are as follows: standard repair, $n = 367$; synthetic mesh, $n = 291$; biological graft, $n = 244$.
All analyses are based on 2-year costs and outcomes.

worth noting in this analysis that the probability of biological graft being the most cost-effective treatment strategy increases somewhat. This is due to a combination of factors, namely (1) higher and significant incremental costs for SM using all of the data; (2) less difference in point estimates of incremental QALYs compared with the base-case analysis. The net result is a slightly higher probability of biological graft being the most cost-effective treatment when compared against the base case. The analysis is not sufficiently different from the base case to change any of the conclusions drawn. In order to provide data for comparison with the trial-based clinical effectiveness analysis, we have presented the scatterplots and CEACs from this analysis for completeness in *Figures 14* and *15*. These results further illustrate the uncertainty in the 2-year data and emphasise that there is no clear cost-effective treatment strategy for prolapse repair based on trial data.

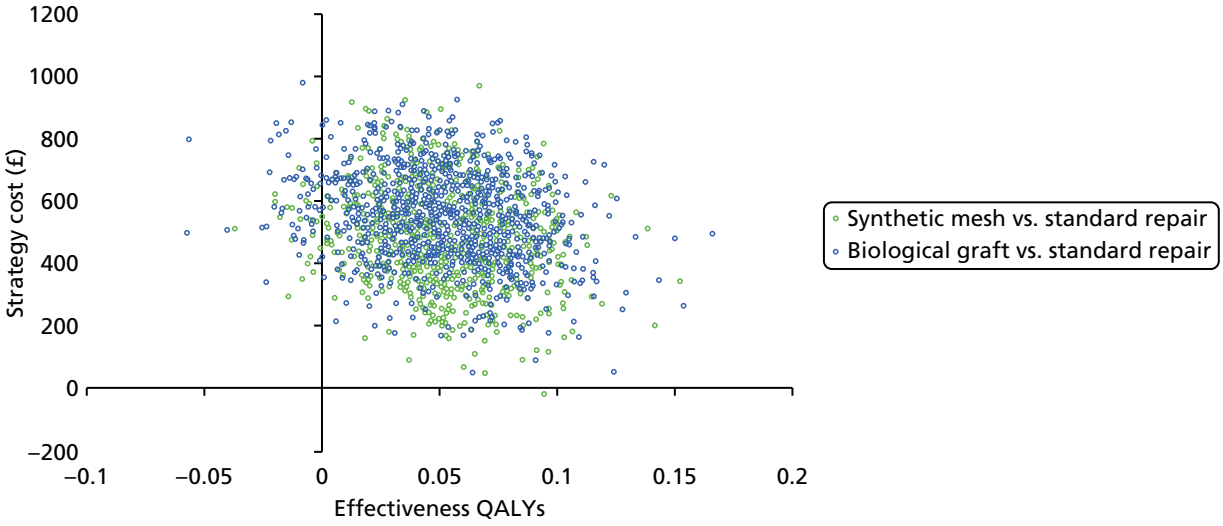


FIGURE 14 Primary trial, RCT1: incremental scatterplot of cost-effectiveness plane – complete case analysis, 2-year outcomes, all randomised women to Primary trial.

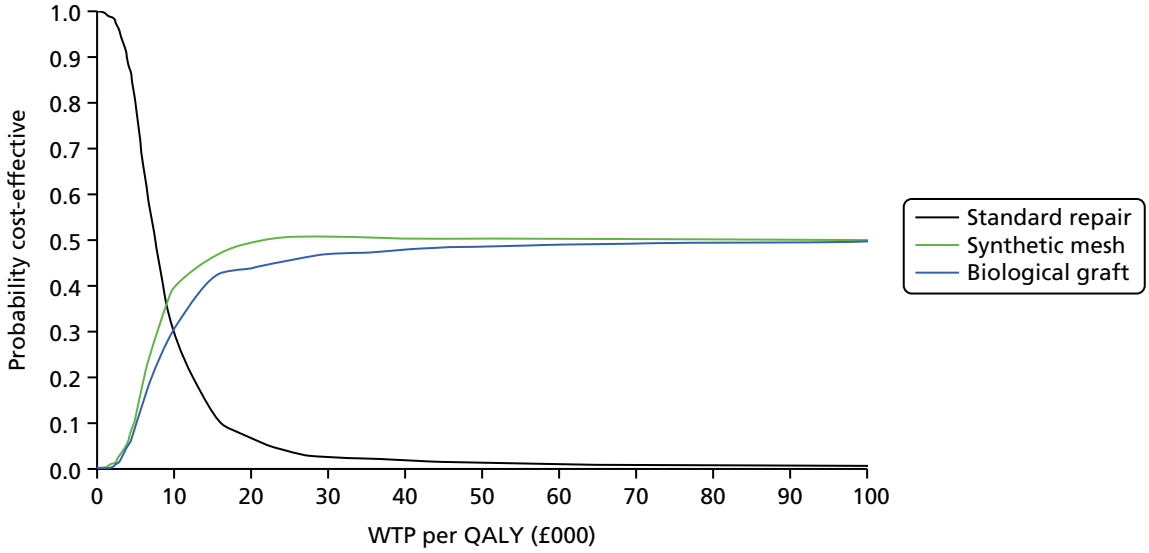


FIGURE 15 Primary trial, RCT1: CEAC – complete case analysis, 2-year outcomes, all randomised women to Primary trial.

Discussion

Summary of findings

For women requiring a primary prolapse surgery procedure, synthetic mesh and biological graft were both more costly procedures, driven by the cost of the mesh materials. There were no differences in costs of time or equipment to perform the respective procedures, nor were there any differences evident in terms of follow-up care required across groups. The estimated ICER for the 2-year follow-up from a NHS perspective was £4493 per QALY gained for synthetic mesh. Considering that society might be willing to pay up to £20,000 or £30,000 for a QALY gain, this result is favourable for synthetic mesh. Biological graft repair had a higher ICER, of £13,537 per QALY relative to standard repair, but was dominated (being more costly and generating fewer QALYs) compared with synthetic mesh. However, these potentially favourable ICERs for synthetic mesh should be interpreted in light of the uncertainty surrounding the results. Based on bootstrapped replications and calculated net benefit statistics, synthetic mesh had the greatest probability of cost-effectiveness at a threshold value of £30,000 WTP for a QALY gained (84%). This indicates that there is a 16% chance that one of the other treatment strategies may be the most cost-effective. There is thus some uncertainty in the data regarding the most cost-effective strategy.

A further level of uncertainty is explored through deterministic sensitivity analysis and, in particular, the impact of missing data on cost-effectiveness conclusions. Using MI models to address any bias or systematic patterns of missingness in the data indicates that mesh remains more costly but no longer generates potential QALY gains, and is thus not a cost-effective treatment strategy using imputed data sets. Overall, across the deterministic analyses undertaken, there is some uncertainty as to the cost-effectiveness of synthetic mesh ranging from 84% for the most favourable base-case analysis and falling to 51% when considering all randomised women who were having a primary repair (analysis comparable with statistical clinical effectiveness analysis), and falling further to 29% for the analysis imputing missing data.

Based on the uncertainty illustrated in the trial-based data and the potential impact of missing data on results, there is no strong evidence to suggest that synthetic mesh is a cost-effective use of resources. A complete case analysis is most favourable to synthetic mesh. Despite potentially favourable ICERs, the estimates are surrounded by considerable uncertainty and definitive conclusions cannot be drawn based on 2-year data alone.

Conclusions of the cost-effectiveness analysis are robust to changes in the model used to analyse the data. We explored a gamma family, log link regression model for costs, as both this and a normal distribution passed the modified Park's test for distributional family. Furthermore, both models had similar AIC values, with the normal having only a slightly lower score, hence its choice for the base-case analysis. However, the conclusions remain broadly robust to the choice of analysis model for the data.

Strengths

A key strength of the study was the UK-wide multicentre design randomising women from 35 centres across the UK. This adds to the external validity and generalisability of the results UK wide. Including a full within-trial cost-effectiveness analysis is a key strength, although data may be of limited value in determining longer-term cost-effectiveness results. The main strength from the within-trial analysis is that a comprehensive microcosting approach was undertaken, further adding to the generalisability of results across participating centres. The incorporation of a wider economic perspective on costs as a secondary analysis adds value – in terms of a broader economic perspective and understanding of the non-health-care costs to women, their families and the economy – more generally of prolapse symptoms and problems. The analysis of QALYs based on EQ-5D-3L patient-level responses follows best practice methods and is another advantage, and will be informative for developing utility weights to populate the decision-analytic model reported in *Chapter 9*.

Limitations

Despite the strengths outlined, there were a number of limitations. First, the estimates of mesh costs are based on average prices across mesh categories and we make no statements about the cost-effectiveness of individual mesh products. This is an area requiring further research to determine if individual products provide better outcomes and more cost-effective treatment options for women. Second, there were some missing data for cost and QALY outcomes. MI of missing cost and EQ-5D-3L data were conducted. Imputation did not alter the cost estimates from the analysis, but did alter the QALY outcomes substantially, removing any potential benefit of mesh procedures. This adds further uncertainty to the trial-based economic analysis and renders it impossible to draw definitive conclusions on cost-effectiveness over a short 2-year time horizon. It should be noted that this short time horizon provides a further limitation, as it fails to address the cost and QoL impacts of any long-term complications or treatment failures and any differences in time to failure/time to experiencing serious complications following initial surgery.

Conclusion

To summarise, over 2-year follow-up, there was no strong evidence on the grounds of cost-effectiveness to recommend the adoption of either synthetic mesh or biological graft for women who were having their first prolapse procedure. There was some evidence that synthetic mesh may improve QoL outcomes but results were subject to biases associated with missing data, which may have over-represented the QALY gains and hence cost-effectiveness outcomes. The probability of cost-effectiveness varied substantially across analyses undertaken, further illustrating the uncertainty in the short-run cost-effectiveness results. It is likely, however, that the cost-effectiveness of mesh procedures will be determined over the longer term, where it will be possible to observe treatment failures, reoperations for prolapse and associated complications. As a result, *Chapter 9* reports on the findings of a Markov cohort decision-analytic model, extrapolating these cost-effectiveness findings over 5 years and making initial projections of time to events such as surgery for prolapse failure and surgery for severe complications. Extended follow-up to 6 years will further provide an opportunity to validate the results of the economic modelling exercise.

Chapter 6 Results: Secondary trial (randomised controlled trial 2, comprehensive cohort 2)

This chapter describes the women who were having a repeat anterior or posterior prolapse repair, both those randomised (RCT2) and those who were not randomised but agreed to be followed up in the CC (CC2). The baseline characteristics of RCT2 and CC2 have been compared in *Chapter 3*; by and large, the populations were similar, suggesting that the findings from the randomised women are generalisable to the larger population of women who were having secondary prolapse repair in the UK.

The flow of women through the study is shown in the CONSORT diagram (*Figure 16*). The women received surgery in 35 centres across the UK (see *Table 4*). Although 154 women were randomised in total, they can be further subdivided according to the panel of operations offered by their surgeon. RCT2, therefore, consists of three strata: RCT2A, in which women could be randomly allocated to any of the three options for this trial; RCT2B, in which women were randomised between two options – standard repair with no mesh and synthetic mesh inlay; and RCT2D, in which they were randomised between no mesh and a mesh kit.

In this chapter, the data are presented according to the strata:

1. *Trial 3* No mesh compared with synthetic mesh inlay [stratum 2A (three-way randomisation) and stratum 2B (two-way randomisation)].
2. *Trial 4* No mesh compared with mesh kit [stratum 2A (three-way randomisation) and stratum 2D (two-way randomisation).

Because the analyses were carried out separately for each trial, some women in the 'no mesh' group from stratum 2A will be represented twice.

Baseline comparability of randomised groups

Women's characteristics at baseline

There were no important differences between the randomised groups of women (trial 3, trial 4; *Table 48*) or between the randomised women in RCT2 and the non-randomised in CC2 (see *Table 5*). In this chapter, the data for the cohort women are provided in the outcome tables for comparison with the randomised groups, but they have not been formally statistically compared. Women who were having secondary repair were much less likely to agree to be randomised (39%) than those in the Primary trial (54%).

The mean ages of the randomised women ranged from 61.4 to 64.3 years (see *Table 48*), on average about 2.5 years older than the women who were having their first repair. The mean BMI was < 30 kg/m^2 for all groups of women, but 10% had a BMI of > 35 kg/m^2. The previous obstetric history was very similar to women who were having their first prolapse operation. All the women were parous. Most babies were born by spontaneous vaginal delivery.

Generic QoL was captured using the EQ-5D-3L validated tool.[25] Women in the synthetic mesh arm in trial 3 had a significantly higher (better) EQ-5D-3L score at baseline than those who were randomised to standard repair (*t*-test $p = 0.024$), whereas in trial 4 the score was lower in the mesh kit arm than the standard repair arm, but this was not significant (*t*-test $p = 0.243$; see *Table 48*).

Regarding previous treatment, 3.8–14.0% were using a vaginal pessary; 34.6–48.0% had already seen a physiotherapist for prolapse symptoms; rather fewer (13.7–22.2%) had seen a physiotherapist for UI; and more than 1 in 10 had used drugs for UI (see *Table 48*). Compared with the women who were having

Type of repair	Secondary 154														
Stratum/ comparison	All 154			Trial 3 107		Trial 4 71		Stratum 2A 91			Stratum 2B 59		Stratum 2D 4		
Treatment arm	Standard repair 56	Synthetic mesh 52	Mesh kit 46	Standard repair 55	Synthetic mesh 52	Standard repair 25	Mesh kit 46	Standard repair 24	Synthetic mesh 24	Mesh kit 43	Standard repair 31	Synthetic mesh 28	Standard repair 1	Mesh kit 3	
Received surgery	56 (100%)	51 (98%)	45 (98%)	55 (100%)	51 (98%)	25 (100%)	45 (98%)	24	24	42	31	27	1	3	
• Standard repair	49 (88%)	9 (18%)	4 (9%)	49 (89%)	9 (18%)	20 (80%)	4 (9%)	20	3	3	29	6	0	1	
• Synthetic mesh	3 (5%)	37 (73%)	7 (16%)	2 (4%)	37 (73%)	1 (4%)	7 (16%)	0	17	7	2	20	1	0	
• Biological graft	1 (2%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (4%)	1 (2%)	1	0	1	0	0	0	0	
• Mesh kit	0 (0%)	2 (4%)	31 (69%)	0 (0%)	2 (4%)	0 (0%)	31 (69%)	0	1	29	0	1	0	2	
• Other surgery	3 (5%)	3 (6%)	2 (4%)	3 (5%)	3 (6%)	3 (12%)	2 (4%)	3	3	2	0	0	0	0	
No surgery	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0	0	1	0	1	0	0	
Baseline questionnaire	55 (98%)	50 (96%)	43 (93%)	54 (98%)	50 (96%)	24 (96%)	43 (93%)	23	24	40	31	26	1	3	
6-month questionnaire	51 (91%)	47 (92%)	43 (96%)	50 (91%)	47 (90%)	22 (88%)	43 (93%)	21	23	41	29	24	1	2	
Withdrawals within 6 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0	0	0	0	0	
Deaths within 6 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0	0	0	0	0	0	0	
12-month short questionnaire	50 (89%)	44 (86%)	44 (98%)	49 (89%)	44 (85%)	21 (84%)	44 (96%)	20	21	41	29	23	1	3	
12-month long questionnaire	47 (84%)	39 (76%)	41 (91%)	46 (84%)	39 (75%)	21 (84%)	41 (89%)	20	17	39	26	22	1	2	
12 month clinic assessment	46 (82%)	44 (86%)	38 (84%)	46 (84%)	44 (85%)	21 (84%)	38 (83%)	21	21	36	25	23	0	2	
Withdrawals within 12 months	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0	0	0	1	0	0	0	
Deaths within 12 months	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (4%)	0 (0%)	1	0	0	0	0	0	0	
24-month questionnaire	44 (79%)	39 (75%)	39 (85%)	43 (78%)	39 (75%)	20 (80%)	39 (85%)	19	18	37	24	21	1	2	
Withdrawals within 24 months	1 (2%)	3 (6%)	2 (4%)	1 (2%)	3 (6%)	0 (0%)	2 (4%)	0	3	2	1	0	0	0	
Deaths within 24 months	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (4%)	0 (0%)	1	0	0	0	0	0	0	

FIGURE 16 CONSORT diagram for Secondary trial. a, *Reasons for non-compliance with randomised allocation*: standard – no prolapse surgery (0); no anterior or posterior repair (3); mesh not required (0); mesh required (3); morbidity/surgical complications (0); patient decided did not want mesh post randomisation (0); theatre not informed/wrong information given (0); mesh not available (0); not enough theatre time (0); consultant not in theatre (0); no reason given for non-compliance (1). b, *Reasons for non-compliance with randomised allocation*: synthetic – no prolapse surgery (0); no anterior or posterior repair (3); mesh not required (0); mesh required (0); morbidity/surgical complications (6); patient decided did not want mesh post randomisation (0); theatre not informed/wrong information given (1); mesh not available (0); not enough theatre time (1); consultant not in theatre (0); no reason given for non-compliance (3). c, *Reasons for non-compliance with randomised allocation*: mesh kit – no prolapse surgery (0); no anterior or posterior repair (3); mesh not required (0); mesh required (0); morbidity/surgical complications (2); patient decided did not want mesh post-randomisation (1); theatre not informed/wrong information given (0); mesh not available (7); not enough theatre time (0); consultant not in theatre (0); no reason given for non-compliance (1). d, Other surgery includes tape for UI, vaginal hysterectomy or suspension; cervical amputation; vault repair.

TABLE 48 Baseline characteristics of participants: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Baseline characteristic	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Number of women	*N* = 55			*N* = 52			*N* = 25			*N* = 46			*N* = 244		
Age	61.9	(8.8)	55	61.4	(9.5)	52	64.3	(8.9)	25	63.1	(11.1)	46	62.1	(10.1)	244
Parity (mean)	2.6	(1.2)	54	2.7	(1.1)	51	2.6	(1.1)	25	2.8	(1.0)	46	2.5	(1.1)	244
Parity (median)	2	(1–6)	54	3	(1–8)	51	2	(1–6)	25	3	(1–5)	46	2	(0–8)	244
BMI (mean)	29.5	(5.2)	52	28.6	(4.2)	43	29.0	(4.2)	25	29.1	(5.2)	38	28.7	(4.8)	220
BMI (median)	29	(21–46)	52	28	(21–39)	43	29	(21–40)	25	28	(91–42)	38	28	(19–44)	220
Delivery mode history															
Spontaneous vaginal delivery	2.2	(1.3)	54	2.1	(1.4)	48	2.3	(1.3)	25	2.5	(1.1)	44	2.2	(1.3)	237
Forceps	0.2	(0.5)	54	0.4	(0.6)	48	0.2	(0.4)	25	0.1	(0.4)	44	0.2	(0.5)	237
Breech	0.1	(0.3)	54	0.0	(0.2)	48	0.1	(0.3)	25	0.0	(0.2)	44	0.0	(0.2)	237
Elective caesarean	0.0	(0.0)	54	0.0	(0.2)	48	0.0	(0.0)	25	0.0	(0.0)	44	0.0	(0.1)	237
Emergency caesarean	0.0	(0.1)	54	0.0	(0.1)	48	0.0	(0.0)	25	0.0	(0.3)	44	0.0	(0.2)	237
Vacuum delivery	0.0	(0.1)	54	0.0	(0.1)	48	0.0	(0.2)	25	0.0	(0.0)	44	0.0	(0.1)	237
EQ-5D															
Score	0.64	(0.30)	52	0.75	(0.16)	50	0.76	(0.18)	24	0.69	(0.24)	42	0.65	(0.26)	213
Previous conservative treatment															
Current vaginal pessary	9.3%	5	54	3.8%	2	52	12.5%	3	24	14.0%	6	43	9.9%	24	242
Physiotherapy for prolapse	36.4%	20	55	34.6%	18	52	48.0%	12	25	36.4%	16	44	32.1%	76	237
Physiotherapy for UI	14.5%	8	55	13.7%	7	51	16.0%	4	25	22.2%	10	45	16.4%	39	238
Drugs for UI	10.9%	6	55	11.5%	6	52	16.0%	4	25	18.2%	8	44	16.4%	39	238

continued

TABLE 48 Baseline characteristics of participants: Secondary trial (*continued*)

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Baseline characteristic	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Previous surgery															
Previous prolapse repair	100.0%	55	55	100.0%	52	52	100.0%	25	25	100.0%	46	46	100.0%	244	244
Anterior	81.8%	45	55	71.2%	37	52	88.0%	22	25	91.3%	42	46	86.1%	210	244
Posterior	60.0%	33	55	59.6%	31	52	44.0%	11	25	45.7%	21	46	57.0%	139	244
Anterior and posterior	41.8%	23	55	30.8%	16	52	32.0%	8	25	37.0%	17	46	43.0%	105	244
Vault	7.3%	4	55	9.6%	5	52	0.0%	0	25	13.0%	6	46	14.8%	36	244
Unknown compartment	1.8%	1	55	0.0%	0	52	4.0%	1	25	2.2%	1	46	1.2%	3	244
Hysterectomy	68.5%	37	54	63.5%	33	52	2.4%	13	24	52.2%	24	46	73.0%	178	244
Vaginal	40.7%	22	54	38.5%	20	52	33.3%	8	24	28.3%	13	46	44.7%	109	244
Cervical amputation	5.6%	3	54	9.6%	5	52	8.3%	2	24	10.9%	5	46	7.0%	17	244
Abdominal	27.8%	15	54	25.0%	13	52	20.8%	5	24	23.9%	11	46	27.0%	66	244
Continence surgery	14.8%	8	54	11.8%	6	51	12.5%	3	24	11.1%	5	45	16.4%	39	238

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

primary surgery, many more had already had a hysterectomy (63.5–68.5%) of which around 35% were carried out via the vaginal route, and 11.1–14.8% had already had continence surgery. All women had had previous anterior or posterior prolapse surgery and were presenting for repeat surgery in at least one of those compartments.

Preoperative prolapse measurements

Women in the randomised groups were comparable in terms of the maximum descent of the three different prolapse compartments. Using qualitative descriptions of prolapse stage to supplement missing POP-Q data, all randomised women were found to have a prolapse stage 2 or greater before surgery (*Table 49*). For the women who had a quantitative score measured using the POP-Q system, women were found to have the leading edge of the prolapse outside the hymen (> 0 cm) most often in the groups randomised to mesh inlay (54.0%) or mesh kit (65.9%) compared with the standard repair groups (38.9%, 50.0%, respectively).

Prolapse symptoms at baseline

Women had noticed symptoms of prolapse for 2.6–3.5 years in total, and had been bothered for 2.2–2.7 years before surgery (*Table 50*). The POP-SS is composed of seven individual prolapse symptoms (each scored from 0 to 4, where '0' is never and '4' is all the time; see *Chapter 2*). At baseline, the mean POP-SS ranged from 13.5 to 15.3 out of a maximum score of 28 (see *Table 50*). All women were deemed to be symptomatic using the criterion of scoring at least one on the Pelvic Organ Prolapse Symptom scale (apart from one woman in CC2). The most common symptom was 'a feeling of something coming down from or in the vagina' and > 90% of women reported this at least occasionally, whereas > 50% had a visible prolapse outside the hymen (see *Table 50*).

As well as the groups being comparable at baseline for the overall score, there were no systematic differences between the groups in any individual prolapse symptoms or other measures of the effect of prolapse on QoL or in modifying women's behaviour to ameliorate the effects of prolapse (see *Table 50*).

Urinary symptoms at baseline

The urinary symptoms reported by women were captured using a variety of validated questionnaires and scales from the ICI Modular Questionnaire suite.[26] Around four in five women had at least some urinary leakage, and this was severe for one in five (*Table 51*).

There were no systematic differences between the groups but urinary symptoms were common in women with secondary prolapse (e.g. around 80% reported some UI). This emphasises the importance of taking into consideration concomitant symptoms when treating women whose primary complaint is prolapse.

Bowel symptoms at baseline

There were no systematic differences between the groups in terms of frequency of bowel movements, constipation, bowel urgency or FI, or in the effect bowel symptoms had on QoL (*Table 52*). Around one-quarter of the women had constipation (classified according to the ROME[30] criteria). Two in five women reported FI at least occasionally, whereas around 1 in 10 had severe FI (sometimes or more often; see *Table 52*).

Vaginal and sexual symptoms at baseline

We used the validated ICIQ-VS and the ICIQ Sexual Matters instruments to capture aspects of vaginal and sexual function.[26] About two-thirds of the women were not sexually active (*Table 53*); of these, over one-third did not have sexually active partners, and the most common reason in the remainder was attributable to their prolapse symptoms. Only six of the randomised women who answered the question reported pain with intercourse (dyspareunia) before surgery (and a further 15 in the non-randomised cohort; see *Table 53*). There were no systematic differences between the groups in terms of these parameters at baseline.

TABLE 49 Preoperative objective measures of prolapse: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
POP-Q measurement/stage	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Number of women	*N* = 55			*N* = 52			*N* = 25			*N* = 46			*N* = 244		
POP-Q measurement (cm)															
Ba (anterior edge)	–0.2	(1.8)	54	–0.1	(2.0)	48	0.1	(2.1)	24	0.7	(2.1)	40	0.3	(2.1)	201
C (cervix/vault)	–4.3	(2.5)	52	–4.4	(3.2)	45	–3.8	(2.3)	22	–3.3	(3.9)	37	–3.3	(3.5)	191
Bp (posterior edge)	–0.5	(1.8)	52	–0.5	(1.9)	49	–0.4	(2.1)	23	–0.5	(2.4)	38	–0.3	(2.1)	194
TVL	8.1	(3.3)	50	8.3	(1.4)	42	7.6	(1.3)	21	8.0	(1.2)	36	8.0	(1.5)	179
Overall POP-Q stage															
0	0.0%	0	55	0.0%	0	52	0.0%	0	25	0.0%	0	45	0.4%	1	227
1	0.0%	0	55	0.0%	0	52	0.0%	0	25	0.0%	0	45	0.9%	2	227
2	76.4%	42	55	71.2%	37	52	68.0%	17	25	55.6%	25	45	60.8%	138	227
3	21.8%	12	55	28.8%	15	52	28.0%	7	25	42.2%	19	45	31.3%	71	227
4	1.8%	1	55	0.0%	0	52	4.0%	1	25	2.2%	1	45	6.6%	15	227
2b, 3 or 4	*38.9%*	*21*	*54*	*54.0%*	*27*	*50*	*50.0%*	*12*	*24*	*65.9%*	*27*	*41*	*57.8%*	*119*	*206*

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

TABLE 50 Prolapse symptoms at baseline: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Symptom	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Number of women	*N* = 54			*N* = 50			*N* = 24			*N* = 43			*N* = 221		
POP-SS	14.3	(5.4)	54	13.7	(5.1)	50	13.5	(5.7)	24	15.3	(5.4)	43	14.9	(5.8)	220
Other measures of prolapse symptoms															
Duration of symptoms (years)	2.6	(3.1)	53	2.8	(3.9)	49	3.5	(4.2)	24	3.1	(2.6)	39	3.8	(5.3)	205
Duration of bother (years)	2.2	(2.9)	52	2.3	(3.6)	48	2.4	(3.9)	24	2.7	(2.5)	39	2.9	(4.1)	201
Number of women symptomatic	100.0%	54	54	100.0%	50	50	100.0%	24	24	100.0%	43	43	99.5%	219	220
Prolapse-related QoL score	6.5	(2.6)	54	7.1	(2.3)	50	5.5	(2.9)	24	7.2	(1.9)	43	6.9	(2.5)	216
Individual prolapse symptoms															
SCD any	90.7%	49	54	92.0%	46	50	87.5%	21	24	100.0%	43	43	94.5%	208	220
SCD freq.	68.5%	37	54	70.0%	35	50	58.3%	14	24	81.4%	35	43	71.4%	157	220
Pain any	77.8%	42	54	78.0%	39	50	87.5%	21	24	86.0%	37	43	85.9%	189	220
Pain freq.	31.5%	17	54	34.0%	17	50	29.2%	7	24	46.5%	20	43	45.0%	99	220
Abdo. any	83.3%	45	54	80.0%	40	50	79.2%	19	24	88.4%	38	43	85.9%	189	220
Abdo. freq.	35.2%	19	54	32.0%	16	50	37.5%	9	24	46.5%	20	43	45.0%	99	220
Back any	77.8%	42	54	70.0%	35	50	83.3%	20	24	72.1%	31	43	82.7%	182	220
Back freq.	40.7%	22	54	32.0%	16	50	33.3%	8	24	30.2%	13	43	34.1%	75	220
Strain blad. any	74.1%	40	54	62.0%	31	50	75.0%	18	24	76.7%	33	43	67.7%	149	220
Strain blad. freq.	22.2%	12	54	30.0%	15	50	20.8%	5	24	27.9%	12	43	29.5%	65	220
Blad. not empty any	88.9%	48	54	76.0%	38	50	91.7%	22	24	90.7%	39	43	82.7%	182	220
Blad. not empty freq.	42.6%	23	54	34.0%	17	50	37.5%	9	24	48.8%	21	43	35.9%	79	220
Bowel not empty any	81.5%	44	54	88.0%	44	50	70.8%	17	24	86.0%	37	43	85.0%	187	220
Bowel not empty freq.	35.2%	19	54	40.0%	20	50	25.0%	6	24	25.6%	11	43	43.2%	95	220

continued

TABLE 50 Prolapse symptoms at baseline: Secondary trial (*continued*)

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Symptom	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Actions necessitated by prolapse symptoms															
Fingers to ease discomfort	18.9%	10	53	14.0%	7	50	16.7%	4	24	14.3%	6	42	16.0%	34	213
Extra hygiene measures	54.9%	28	51	48.0%	24	50	52.2%	12	23	51.2%	21	41	56.1%	120	214
Fingers to help empty bladder	5.7%	3	53	2.0%	1	50	12.5%	3	24	4.7%	2	43	3.7%	8	214
Fingers to help empty bowel	5.7%	3	53	8.0%	4	50	4.2%	1	24	2.4%	1	41	8.3%	18	217
Digital evacuation of bowel	9.6%	5	52	6.1%	3	49	8.3%	2	24	2.4%	1	42	5.1%	11	215

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome; *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality of life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

Bowel symptoms

Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

TABLE 51 Urinary symptoms at baseline: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Symptom	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Number of women	*N* = 54			*N* = 50			*N* = 24			*N* = 43			*N* = 221		
Any incontinence	83.0%	44	53	76.0%	38	50	83.3%	20	24	83.7%	36	43	74.7%	165	221
Incontinence-related QoL score	7.3	(5.2)	53	7.2	(5.8)	49	6.2	(4.2)	24	8.4	(5.9)	43	7.0	(5.8)	220
Severe incontinence	15.1%	8	53	20.4%	10	49	8.3%	2	24	25.6%	11	43	20.0%	44	220
ICIQ-UI-SF score	3.6	(3.2)	52	3.6	(3.5)	50	2.6	(3.0)	24	4.3	(3.5)	42	3.5	(3.3)	211
Stress UI	23.5%	12	51	20.0%	9	45	16.7%	4	24	14.6%	6	41	18.8%	36	192
Urgency UI	7.5%	4	53	8.0%	4	50	4.2%	1	24	16.3%	7	43	10.7%	23	215
Overactive bladder	3.8%	2	53	6.0%	3	50	4.2%	1	24	11.6%	5	43	9.0%	19	211
ICIQ-FLUTS filling score	6.0	(2.9)	52	5.6	(3.1)	50	5.6	(2.3)	23	6.3	(2.8)	43	6.0	(3.1)	208
ICIQ-FLUTS voiding score	3.3	(2.6)	53	3.6	(2.8)	50	2.7	(2.1)	23	3.3	(2.7)	43	3.2	(2.8)	212
ICIQ-FLUTS incontinence score	5.8	(4.0)	49	5.8	(4.2)	45	4.8	(3.2)	23	6.4	(4.3)	41	6.2	(4.3)	190

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

TABLE 52 Bowel symptoms at baseline: Secondary trial

Symptoms	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
	Standard repair (*N* = 54 women)			Synthetic mesh (*N* = 50 women)			Standard repair (*N* = 24 women)			Mesh kit (*N* = 43 women)			CC2 (*N* = 221 women)		
Bowel frequency															
> 3 times a day	2.2%	1	45	5.1%	2	39	4.8%	1	21	4.9%	2	41	3.2%	6	188
1–3 times a day	37.8%	17	45	30.8%	12	39	28.6%	6	21	24.4%	10	41	33.5%	63	188
About once a day	35.6%	16	45	35.9%	14	39	42.9%	9	21	48.8%	20	41	45.2%	85	188
Once every 2–3 days	20.0%	9	45	23.1%	9	39	19.0%	4	21	17.1%	7	41	14.9%	28	188
Weekly or less	4.4%	2	45	5.1%	2	39	4.8%	1	21	4.9%	2	41	3.2%	6	188
Constipation	23.1%	12	52	36.0%	18	50	13.0%	3	23	14.3%	6	42	31.0%	66	213
Bowel urgency	11.3%	6	53	12.0%	6	50	4.3%	1	23	4.8%	2	42	8.6%	19	220
FI (any)	37.0%	20	54	40.0%	20	50	37.5%	9	24	40.5%	17	42	36.4%	80	220
Passive FI	75.0%	15	20	80.0%	16	20	88.9%	8	9	94.1%	16	17	81.3%	65	80
Active FI	25.0%	5	20	20.0%	4	20	11.1%	1	9	5.9%	1	17	18.8%	15	80
Severe FI	13.0%	7	54	12.0%	6	50	16.7%	4	24	7.1%	3	42	11.4%	25	220
Bowel symptoms QoL score	3.4	(3.1)	50	3.8	(3.4)	48	2.9	(3.4)	21	3.9	(2.9)	42	3.6	(3.1)	212

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: Any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 53 Vaginal and sexual symptoms at baseline: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Symptom	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Number of women	*N* = 54			*N* = 50			*N* = 24			*N* = 43			*N* = 221		
Vaginal															
ICIQ-VS score	21.1	(10.0)	49	22.2	(9.5)	46	17.5	(9.2)	23	23.4	(7.8)	38	23.8	(9.6)	188
Vaginal symptoms QoL score	4.9	(3.5)	51	5.4	(3.4)	47	3.9	(3.4)	23	5.7	(3.0)	40	5.4	(3.2)	204
Vagina too tight	3.8%	2	52	0.0%	0	47	0.0%	0	23	2.6%	1	39	5.6%	11	197
Sexual															
Sex life at present (yes)	30.2%	16	53	52.0%	26	50	25.0%	6	24	34.1%	14	41	29.9%	64	214
Reason for no sex life															
No partner	29.7%	11	37	41.7%	10	24	38.9%	7	18	37.0%	10	27	27.3%	41	150
Vaginal symptoms	2.7%	1	37	0.0%	0	24	0.0%	0	18	0.0%	0	27	5.3%	8	150
Prolapse symptoms	43.2%	16	37	29.2%	7	24	33.3%	6	18	33.3%	9	27	38.7%	58	150
Other reason	18.9%	7	37	25.0%	6	24	22.2%	4	18	25.9%	7	27	24.7%	37	150
Reason not given	5.4%	2	37	4.2%	1	24	5.6%	1	18	3.7%	1	27	4.0%	6	150
Dyspareunia	4.5%	1	22	15.6%	5	32	0.0%	0	8	0.0%	0	20	15.5%	15	97
ICI Sexual Matters score	23.1	(13.7)	21	25.7	(12.5)	32	20.6	(13.8)	7	27.3	(12.8)	20	24.4	(15.5)	95
Sex life QoL score	7.1	(3.4)	24	7.2	(2.6)	32	6.1	(3.3)	9	8.0	(1.8)	22	6.8	(3.3)	112

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *Dyspareunia at baseline*: denominator includes number of women who were sexually active and those who did not have a sex life because of prolapse symptoms; *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

Surgery planned before surgery and actually received during surgery

Planned operations

The most common operation (anticipated for about half of the women) was anterior repair only, with about one-quarter planning to have a posterior repair only, whereas a further quarter were having both. Planned concomitant surgery included 8.0–21.7% of women who were thought to need a vaginal hysterectomy, and a further 19.2–28.0% requiring a vault repair. Finally, 2.2–7.3% were thought to require a continence procedure.

Surgery actually received

Most women received the surgery planned (see *Figure 16* and *Table 54*). In trial 3, in the standard repair group, more women (27.3%) had a combined anterior/posterior repair than in the other two groups (synthetic mesh 13.7% and mesh kit 13.3%) and more had a concomitant vault repair (25.5% compared with 9.8% and 13.3%, respectively) (see *Table 54*). It is possible that knowledge of the allocated intervention influenced the surgery actually carried out, but the numbers were too small to draw definite conclusions.

Compliance with randomised allocation

Two women did not receive surgery at all (see *Figure 16*). Ten women were not thought to need an anterior or posterior repair once anaesthetised because the surgeon did not deem it necessary, and therefore they were unable to carry out the randomised allocation (see *Figure 16*).

Three women randomised to standard repair alone received a mesh inlay because the surgeon thought it was clinically indicated, but none had a mesh kit. In trial 3, a further 14/51 women failed to receive their allocated (randomised) intervention in the synthetic mesh arm: this was most often due to surgical complications. Similarly in trial 4 a further 14/45 women did not receive their allocated mesh kit, most often ($n = 7$) because the kit was not available on the day of surgery (see *Figure 16*).

Summary

Overall there were no important differences in clinical characteristics at baseline between the women randomised to the two groups in trial 3 (standard repair vs. synthetic mesh inlay) or in trial 4 (standard repair vs. mesh kit).

Outcomes

Description of surgery and operative characteristics

There were no statistically significant differences in the duration of surgery (*Table 55*). Blood loss was higher in the synthetic mesh group (by 36.8 ml), but not significantly so in the mesh kit group, compared with standard repair. The mean length of stay ranged from 2.4 to 3.0 days, with no differences between the randomised groups (see *Table 55*). This time included any preoperative days if the women were admitted a day before surgery.

Serious related adverse effects in first and second years

The diagnoses in *Tables 57* and *58* are confined to those that met our definition of 'serious' (see *Chapter 2*). An adverse effect (AE) was defined as 'serious' (SAE) if it was related to prolapse surgery and resulted in death; was life-threatening; required hospitalisation or prolongation of an existing admission; resulted in significant disability/incapacity; or was otherwise considered medically significant by the investigator. If it did not meet the requirement for 'serious' it was classed as 'other'.

TABLE 54 Planned surgery and surgery actually performed: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Type of surgery	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Planned surgery															
Number of women	*N* = 55			*N* = 52			*N* = 25			*N* = 46			*N* = 244		
Prolapse procedure															
Anterior repair	43.6%	24	55	44.2%	23	52	56.0%	14	25	52.2%	24	46	45.9%	112	244
Posterior repair	25.5%	14	55	28.8%	15	52	20.0%	5	25	23.9%	11	46	26.6%	65	244
Anterior and posterior repair	27.3%	15	55	13.7%	7	51	20.0%	5	25	13.3%	6	45	22.1%	53	240
Upper compartment repair only	0.0%	0	55	0.0%	0	52	0.0%	0	25	0.0%	0	46	0.0%	0	244
Concomitant prolapse procedure															
Vaginal hysterectomy	9.1%	5	55	11.5%	6	52	8.0%	2	25	21.7%	10	46	6.6%	16	244
Cervical amputation	0.0%	0	55	0.0%	0	52	0.0%	0	25	0.0%	0	46	0.8%	2	244
Abdominal hysterectomy	0.0%	0	55	1.9%	1	52	0.0%	0	25	0.0%	0	46	0.8%	2	244
Vault repair	27.3%	15	55	19.2%	10	52	28.0%	7	25	21.7%	10	46	27.0%	66	244
Continence procedure	7.3%	4	55	3.8%	2	52	4.0%	1	25	2.2%	1	46	6.6%	16	244
Surgery actually performed															
Number of women	*N* = 55			*N* = 51			*N* = 25			*N* = 45			*N* = 240		
Actual prolapse procedure															
Anterior repair only	38.2%	21	55	49.0%	25	51	44.0%	11	25	51.1%	23	45	43.8%	105	240
Posterior repair only	29.1%	16	55	31.4%	16	51	24.0%	6	25	31.1%	14	45	26.7%	64	240
Anterior and posterior repair	27.3%	15	55	13.7%	7	51	20.0%	5	25	13.3%	6	45	22.1%	53	240
Neither	5.5%	3	55	5.9%	3	51	12.0%	3	25	4.4%	2	45	7.5%	18	240

continued

TABLE 54 Planned surgery and surgery actually performed: Secondary trial (*continued*)

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Type of surgery	Standard repair			Synthetic mesh			Standard repair			Mesh kit			CC2		
Concomitant prolapse procedure															
Vaginal hysterectomy	7.3%	4	55	7.8%	4	51	12.0%	3	25	8.9%	4	45	7.1%	17	240
Abdominal hysterectomy	0.0%	0	55	0.0%	0	51	0.0%	0	25	0.0%	0	45	0.4%	1	240
Cervical amputation	1.8%	1	55	2.0%	1	51	4.0%	1	25	0.0%	0	45	1.3%	3	240
Uterine suspension	0.0%	0	55	0.0%	0	51	0.0%	0	25	4.4%	2	45	3.8%	9	240
Vault repair	25.5%	14	55	9.8%	5	51	28.0%	7	25	13.3%	6	45	26.3%	63	240
Continence procedure	7.3%	4	55	3.9%	2	51	8.0%	2	25	0.0%	0	45	6.7%	16	240

Dichotomous variables are presented as '% *n* *N*'.

TABLE 55 Description of surgical characteristics and protocols: Secondary trial

	Trial 3: standard vs. synthetic						Trial 4: standard vs. mesh kit								
Surgical characteristic	**Standard repair**			**Synthetic mesh**			**Standard repair**			**Mesh kit**			**CC2**		
Received surgery	*N* = 55			*N* = 51			*N* = 25			*N* = 45			*N* = 240		
Grade of staff															
Consultant	78.2%	43	55	84.0%	42	50	76.0%	19	25	93.3%	42	45	85.8%	206	240
Specialty doctor	9.1%	5	55	6.0%	3	50	4.0%	1	25	4.4%	2	45	3.8%	9	240
Specialty doctor supervised	100.0%	5	5	100.0%	3	3	100.0%	1	1	50.0%	1	2	57.1%	4	7
Registrar/junior	12.7%	7	55	10.0%	5	50	20.0%	5	25	2.2%	1	45	10.4%	25	240
Registrar/junior supervised	85.7%	6	7	100.0%	5	5	80.0%	4	5	100.0%	1	1	87.5%	21	24
Duration (minutes)	70.4	(28.7)	55	74.0	(23.7)	48	66.7	(33.5)	25	76.2	(28.3)	45	82.7	(40.8)	234
Estimated blood loss (ml)	108.4	(56.9)	51	145.2	(103.3)	48	107.5	(66.5)	24	126.6	(101.1)	41	116.1	(112.4)	223
Length of stay (days)	2.6	(2.0)	54	3.0	(2.2)	49	2.4	(1.5)	25	2.8	(1.8)	45	2.6	(1.4)	240
Type of anaesthetic															
General	81.8%	45	55	82.4%	42	51	72.0%	18	25	84.4%	38	45	83.1%	197	237
Spinal	21.8%	12	55	17.6%	9	51	28.0%	7	25	15.6%	7	45	20.3%	48	237
Local	9.1%	5	55	2.0%	1	51	16.0%	4	25	11.1%	5	45	5.1%	12	237
Prophylactic antibiotic	96.4%	53	55	94.0%	47	50	92.0%	23	25	91.1%	41	45	95.2%	220	231
Vaginal pack inserted	80.8%	42	52	84.0%	42	50	73.9%	17	23	88.9%	40	45	73.6%	170	231
Catheter inserted	90.9%	50	55	94.1%	48	51	84.0%	21	25	100.0%	45	45	94.5%	225	238
Suprapubic	0.0%	0	50	0.0%	0	48	4.8%	1	21	4.4%	2	45	2.2%	5	224
Urethral	100.0%	50	50	100.0%	48	48	95.2%	20	21	95.6%	43	45	97.3%	218	224
Both	0.0%	0	50	0.0%	0	48	0.0%	0	21	0.0%	0	45	0.4%	1	224

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

TABLE 56 Comparison of surgical characteristics: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
Surgical characteristic	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Number of women who received surgery	*N* = 55			*N* = 51						*N* = 25			*N* = 45						*N* = 240		
Duration of surgery (minutes)	70.4	(28.7)	55	74.0	(23.7)	48	3.65	–5.73 to 13.03	0.440	66.7	(33.5)	25	76.2	(28.3)	45	8.28	–6.05 to 22.61	0.250	82.7	(40.8)	234
Length of stay	2.6	(2.0)	54	3.0	(2.2)	49	0.34	–0.44 to 1.13	0.385	2.4	(1.5)	25	2.8	(1.8)	45	0.51	–0.18 to 1.20	0.145	2.6	(1.4)	240
Blood loss (ml)	108.4	(56.9)	51	145.2	(103.3)	48	38.80	7.3 to 70.3	0.017	107.5	(66.5)	24	126.6	(101.1)	41	27.6	–9.3 to 64.4	0.138	116.1	(112.4)	223

Continuous variables are presented as 'mean (SD) *N*'.

TABLE 57 Serious and related adverse effects within first and second years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Number of women at 1 year	*N* = 55			*N* = 52						*N* = 25			*N* = 46						*N* = 244		
Intraoperative complications																					
Injury to organs	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Excess blood loss	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Blood transfusion	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	1	244
Anaesthetic complications	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Death	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Serious adverse effects in first year																					
Thrombosis	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	1	244
Infection	5.5%	3	55	3.8%	2	52	0.70	0.12 to 3.96	0.686	4.0%	1	25	0.0%	0	46	N/A	N/A	N/A	2.9%	7	244
Pain	7.3%	4	55	1.9%	1	52	0.28	0.03 to 2.35	0.239	8.0%	2	25	2.2%	1	46	0.20	0.02 to 2.04	0.176	1.2%	3	244
Urinary retention	3.6%	2	55	1.9%	1	52	0.50	0.05 to 5.25	0.562	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	1.2%	3	244
Bowel obstruction	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Constipation	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Excess blood loss	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Vaginal adhesions	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Haematoma	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	2.0%	5	244
Skin tags	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Granulation tissue	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.0%	0	244
Urinary tract symptoms	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.8%	2	244

continued

TABLE 57 Serious and related adverse effects within first and second years: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
Death	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Any serious adverse effects (excluding mesh exposure)	12.7%	7	55	9.6%	5	52	1.05	0.66 to 1.68	0.831	12.0%	3	25	6.5%	3	46	0.49	0.11 to 2.16	0.345	7.8%	19	244
Number of women at 2 years	*N* = 55			*N* = 52						*N* = 25			*N* = 46						*N* = 244		
Serious adverse effects in second year																					
Thrombosis	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Infection	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Pain	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	1	244
Urinary retention	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Bowel obstruction	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Constipation	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Excess blood loss	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Vaginal adhesions	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Haematoma	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Skin tags	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Granulation tissue	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	1	244
Urinary tract symptoms	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Death	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Any serious adverse effects (excluding mesh exposure)	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	4.3%	2	46	N/A	N/A	N/A	1.2%	3	244

N/A, not applicable.
Dichotomous variables are presented as '% *n N*'.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 58 Other related adverse effects within first and second years: Secondary trial

Adverse effect	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
Number of women	*N* = 55			*N* = 52						*N* = 25			*N* = 46						*N* = 244		
Intraoperative complications																					
Injury to organs	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Excess blood loss	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Blood transfusion	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Anaesthetic complication	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Other adverse effects in first year																					
Thrombosis	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	2.5%	0	244
Infection	3.6%	2	55	7.7%	4	52	2.12	0.41 to 10.87	0.367	4.0%	1	25	2.2%	1	46	0.61	0.04 to 9.08	0.718	0.8%	6	244
Pain	1.8%	1	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	2	244
Urinary retention	3.6%	2	55	1.9%	1	52	0.53	0.05 to 5.58	0.600	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.0%	0	244
Bowel obstruction	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Constipation	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Excess blood loss	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.8%	0	244
Vaginal adhesions	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	2	244
Haematoma	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	1	244
Skin tags	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Granulation tissue	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	0	244
Urinary tract symptoms	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	1	244
Any other adverse effects (excluding mesh exposure)	9.1%	5	55	13.5%	7	52	1.23	0.43 to 3.46	0.701	4.0%	1	25	4.3%	2	46	1.16	0.12 to 11.77	0.897	0.4%	12	244

continued

TABLE 58 Other related adverse effects within first and second years: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
Adverse effect	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Number of women	*N* = 55			*N* = 52						*N* = 25			*N* = 46						*N* = 244		
Other adverse effects in second year																					
Thrombosis	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Infection	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Pain	0.0%	0	55	1.9%	1	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.4%	1	244
Urinary retention	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Bowel obstruction	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	2.2%	1	46	N/A	N/A	N/A	0.0%	0	244
Constipation	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Excess blood loss	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Vaginal adhesions	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.4%	1	244
Haematoma	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Skin tags	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Granulation tissue	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Urinary tract symptoms	0.0%	0	55	0.0%	0	52	N/A	N/A	N/A	0.0%	0	25	0.0%	0	46	N/A	N/A	N/A	0.0%	0	244
Any other adverse effects (excluding mesh exposure)	0.0%	0	55	3.8%	2	52	N/A	N/A	N/A	0.0%	0	25	4.3%	2	46	N/A	N/A	N/A	1.2%	3	244

N/A, not applicable.
Dichotomous variables are presented as '% *n* *N*'.

Non-mesh serious adverse effects in first and second years

Very few women had any serious adverse effects, excluding mesh exposure (see *Table 57*). The overall number of women experiencing at least one serious adverse effect during the first year after surgery ranged from 6.5% (in the mesh kit group) to 12.7% (in the standard repair group of trial 3; see *Table 57*). One woman in the synthetic mesh inlay group experienced excess blood loss during surgery (> 500 ml) and one in the mesh kit group required a blood transfusion. Individual serious events thereafter were rare, the most common being infection, pain and urinary retention, all of which are common after gynaecological surgery, generally of short duration and easily treated. There were no statistically significant differences between the randomised groups.

Only two women had any serious adverse effects in the second year: both were in the mesh kit group.

Other non-mesh adverse effects in first and second years

Fifteen women experienced at least one minor adverse effect in the first year and a further four in the second year (see *Table 58*).

There were no statistically significant differences between the randomised groups in either trial 3 or trial 4 in terms of any adverse effects (excluding mesh exposure), as there were very few events.

Prolapse symptoms at 6 months, 1 year and 2 years

The women's report of prolapse symptoms, measured using the POP-SS at 6 months, 1 year and 2 years, was less than half of the preoperative level (mean score before surgery 14.5/28; at 6 months 5.9/28; at 1 year 6.3/28; at 2 years 5.2/28; see *Tables 50* and *59*). There were no differences between the randomised groups at any outcome time point.

Specifically the primary clinical outcome was the POP-SS at 1 year (*Table 59*).

1. In trial 3, the MD in the POP-SSs for standard repair (6.6, SD 6.0) compared with synthetic mesh (6.1, SD 6.4), adjusted for baseline values and minimisation variables, and based on data only from women in stratum 2A (three-way randomisation) and stratum 2B (two-way randomisation), was –0.41 (95% CI –2.92 to 2.11).
2. In trial 4, the MD for standard repair (6.6, SD 5.5) compared with mesh kit (5.9, SD 5.3), adjusted for baseline values and minimisation variables, and based on data only from women in stratum 2A (three-way randomisation) and stratum 2D (two-way randomisation), was –1.21 (95% CI –4.13 to 1.72).

At 2 years:

1. In trial 3, the MD in the POP-SSs for standard repair (4.8, SD 5.0) compared with synthetic mesh (5.4, SD 5.5), adjusted for baseline values and minimisation variables, and based on data only from women in stratum 2A (three-way randomisation) and stratum 2B (two-way randomisation), was 0.58 (95% CI –1.68 to 2.84).
2. In trial 4, the MD for standard repair (3.9, SD 4.4) compared with mesh kit (5.4, SD 5.3), adjusted for baseline values and minimisation variables, and based on data only from women in stratum 2A (three-way randomisation) and stratum 2D (two-way randomisation), was 0.65 (95% CI –2.20 to 3.50).

Thus, the difference between the groups was small and not statistically significant. The size of the CIs included the prespecified minimal clinically important difference of three, which we considered to be clinically important for the Secondary trial.

We conclude that, although prolapse surgery was very effective in reducing women's prolapse symptoms, the trials were not powered to rule in or out whether or not the use of synthetic mesh inlay or a mesh kit provided additional benefit for this outcome in women who were having a repeat repair.

TABLE 59 Prolapse symptom score and QoL at 6 months, 1 year and 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit										
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
6-month outcomes																					
Number of women at 6 months	*N* = 50			*N* = 47						*N* = 22			*N* = 43						*N* = 214		
POP-SS at 6 months	5.5	(5.5)	50	5.8	(5.9)	47	0.35	–1.80 to 2.50	0.746	4.8	(5.3)	22	6.2	(5.6)	43	0.29	–2.59 to 3.16	0.840	6.5	(5.8)	214
Symptomatic prolapse	76.0%	38	50	87.2%	41	47	1.13	0.91 to 1.42	0.273	77.3%	17	22	90.7%	39	43	1.11	0.73 to 1.70	0.613	15.4%	33	214
Prolapse-related QoL score	1.9	(2.9)	49	2.2	(2.9)	46	0.20	–1.00 to 1.40	0.743	1.7	(3.2)	22	2.2	(2.6)	43	0.14	–1.50 to 1.79	0.861	87.4%	187	214
1-year outcomes																					
Number of women at 1 year	*N* = 49			*N* = 44						*N* = 21			*N* = 44						*N* = 216		
POP-SS at 1 year	6.6	(6.0)	49	6.1	(6.4)	44	–0.41	–2.92 to 2.11	0.747	6.6	(5.5)	21	5.9	(5.3)	44	–1.21	–4.13 to 1.72	0.408	7.2	(5.9)	215
Symptomatic	81.6%	40	49	88.6%	39	44	1.05	0.82 to 1.33	0.714	90.5%	19	21	86.4%	38	44	0.93	0.67 to 1.28	0.638	90.2%	194	215
Prolapse-related QoL score	2.5	(2.9)	47	3.0	(3.4)	44	0.43	–0.90 to 1.75	0.522	2.0	(2.6)	21	2.3	(2.8)	43	–0.31	–1.99 to 1.36	0.706	2.9	(3.0)	209
2-year outcomes																					
Number of women at 2 years	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		
POP-SS 2 years	4.8	(5.0)	43	5.4	(5.5)	39	0.58	–1.68 to 2.84	0.607	3.9	(4.4)	20	5.4	(5.3)	39	0.65	–2.20 to 3.50	0.642	7.1	(6.1)	189
Symptomatic	83.7%	36	43	82.1%	32	39	1.00	0.80 to 1.24	0.981	85.0%	17	20	76.9%	30	39	0.92	0.63 to 1.33	0.655	84.7%	160	189
Prolapse-related QoL score	1.7	(2.4)	41	2.4	(2.7)	36	0.38	–0.84 to 1.60	0.529	1.5	(2.6)	18	2.5	(2.7)	37	0.32	–1.45 to 2.09	0.712	3.2	(3.1)	177

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome; *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

The lack of enough evidence of a difference between the groups was similar when we analysed:

- data from individual prolapse symptoms (whether measured as 'any' or occurring 'most or all of the time' (*Table 60*);
- the proportion of women who had at least one prolapse symptom ('symptomatic');
- the prolapse-related QoL score measured as the interference of prolapse symptoms on everyday life, *and*
- the need to undertake extra hygiene measures or manoeuvres to ease discomfort, or to assist pelvic floor functions such as emptying the bladder or bowel (see *Table 60*).

All of these measures demonstrated significant improvements from before surgery, but not enough evidence of difference between the randomised groups in either trial at any time point.

The improvement at 1 year was maintained at 2 years, with respect to all of the prolapse and QoL outcomes measured. However, there were still no statistically significant differences between the randomised groups in either trial at 2 years. The improvement in the cohort women was similar.

EuroQol-5 Dimensions (3-level version)

There were no statistically significant differences between the randomised groups in the generic QoL scores at 6 months, 1 year or 2 years in either trial 3 or trial 4, but the sample size was too small to differentiate reliably between the groups (*Table 61*). However, the score improved from baseline levels in all the groups of women.

Specifically, the EQ-5D-3L scores at 1 year were compared (see *Table 61*).

1. In trial 3 the MD in the EQ-5D-3L scores for standard repair (0.74, SD 0.30) compared with synthetic mesh inlay (0.83, SD 0.22), adjusted for baseline values and, based on data only from women in stratum 2A (three-way randomisation) and stratum 2B (two-way randomisation), was 0.03 (95% CI –0.07 to 0.14).
2. In trial 4, the MD for standard repair (0.79, SD 0.27) compared with mesh kit (0.83, SD 0.19), adjusted for baseline values and, based on data only from women in stratum 2A (three-way randomisation) and stratum 2D (two-way randomisation), was 0.05 (95% CI –0.07 to 0.17).

The EQ-5D-3L scores at 2 years showed:

1. In trial 3, the MD in the EQ-5D-3L scores for standard repair (0.76, SD 0.29) compared with synthetic mesh inlay (0.82, SD 0.19), adjusted for baseline values and, based on data only from women in stratum 2A (three-way randomisation) and stratum 2B (two-way randomisation) was 0.00 (95% CI –0.11 to 0.11).
2. In trial 4, the MD for standard repair (0.76, SD 0.29) compared with mesh kit (0.87, SD 0.14), adjusted for baseline values and, based on data only from women in stratum 2A (three-way randomisation) and stratum 2D (two-way randomisation), was 0.13 (95% CI 0.02 to 0.25).

The findings from the cohort women were similar. Although there was a statistically significant difference in trial 4, with women who were having a mesh kit having a higher (better) QoL score than the standard repair group even after adjustment for baseline imbalances, it may have been a chance finding and its clinical significance is uncertain. This outcome is further explored in the section on economic outcomes in *Chapter 7*, and in the modelling *Chapter 9*.

Urinary symptoms

Detailed information on urinary symptoms was obtained at baseline, 1 year and 2 years. The proportion of women who had concomitant continence surgery ranged from 0.0% to 8.0% (see *Table 54*). There was a decrease of > 10% in the proportion of women who had any UI [from 81% at baseline (see *Table 51*) to 69% at 1 year (*Table 62*)] and the proportion with severe UI more than halved (from 21% to 8%).

TABLE 60 Individual prolapse symptoms at 6 months, 1 year and 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit												
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Six-month outcomes																						
Number of women at 6 months	*N* = 50			*N* = 47						*N* = 22			*N* = 43						*N* = 214		
Individual prolapse symptoms																						
SCD any	36.0%	18	50	44.7%	21	47	1.16	0.71 to 1.89	0.546	40.9%	9	22	37.2%	16	43	0.68	0.33 to 1.37	0.276	0.9	(1.2)	214
SCD freq.	10.0%	5	50	8.5%	4	47	0.93	0.27 to 3.22	0.906	9.1%	2	22	18.6%	8	43	1.29	0.29 to 5.76	0.743	44.9%	96	214
Pain any	26.0%	13	50	36.2%	17	47	1.28	0.70 to 2.33	0.421	31.8%	7	22	34.9%	15	43	0.98	0.47 to 2.06	0.956	0.8	(1.1)	214
Pain freq.	4.0%	2	50	6.4%	3	47	1.38	0.25 to 7.46	0.710	9.1%	2	22	14.0%	6	43	1.40	0.32 to 6.15	0.655	43.0%	92	214
Abdo. any	32.0%	16	50	29.8%	14	47	1.01	0.56 to 1.81	0.980	27.3%	6	22	37.2%	16	43	1.07	0.48 to 2.40	0.874	0.8	(1.0)	214
Abdo. freq.	4.0%	2	50	8.5%	4	47	2.25	0.43 to 11.65	0.334	4.5%	1	22	9.3%	4	43	1.66	0.21 to 13.12	0.629	45.3%	97	214
Back any	46.0%	23	50	44.7%	21	47	1.11	0.74 to 1.66	0.627	40.9%	9	22	27.9%	12	43	0.73	0.38 to 1.40	0.342	0.9	(1.1)	214
Back freq.	14.0%	7	50	14.9%	7	47	1.50	0.63 to 3.55	0.355	4.5%	1	22	9.3%	4	43	2.67	0.36 to 19.99	0.340	48.1%	103	214
Strain blad. any	36.0%	18	50	34.0%	16	47	0.96	0.56 to 1.65	0.878	36.4%	8	22	37.2%	16	43	1.10	0.57 to 2.14	0.776	0.7	(1.0)	214
Strain blad. freq.	4.0%	2	50	10.6%	5	47	3.12	0.60 to 16.39	0.178	0.0%	0	22	4.7%	2	43	N/A	N/A	N/A	39.7%	85	214
Blad. not empty any	58.0%	29	50	48.9%	23	47	0.87	0.58 to 1.29	0.486	50.0%	11	22	67.4%	29	43	1.30	0.79 to 2.16	0.302	1.1	(1.2)	214
Blad. not empty freq.	10.0%	5	50	19.1%	9	47	2.22	0.85 to 5.81	0.105	13.6%	3	22	9.3%	4	43	0.64	0.17 to 2.43	0.509	61.2%	131	214
Bowel not empty any	54.0%	27	50	57.4%	27	47	1.02	0.73 to 1.42	0.905	45.5%	10	22	74.4%	32	43	1.42	0.86 to 2.33	0.173	1.3	(1.2)	214
Bowel not empty freq.	16.0%	8	50	10.6%	5	47	0.57	0.21 to 1.51	0.258	18.2%	4	22	18.6%	8	43	1.05	0.40 to 2.73	0.920	68.7%	147	214
Digital evacuation of bowel																					

Symptom	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
1-year outcomes																					
Number of women at 1 year	*N* = 49			*N* = 44						*N* = 21			*N* = 44						*N* = 216		
Individual prolapse symptoms																					
SCD any	44.9%	22	49	40.9%	18	44	0.91	0.58 to 1.43	0.680	57.1%	12	21	36.4%	16	44	0.57	0.29 to 1.10	0.094	49.3%	106	215
SCD freq.	20.4%	10	49	11.4%	5	44	0.52	0.20 to 1.35	0.177	23.8%	5	21	6.8%	3	44	0.24	0.06 to 1.00	0.049	15.3%	33	215
Pain any	30.6%	15	49	31.8%	14	44	0.98	0.54 to 1.77	0.937	28.6%	6	21	36.4%	16	44	1.34	0.59 to 3.03	0.485	40.9%	88	215
Pain freq.	14.3%	7	49	9.1%	4	44	0.64	0.21 to 1.94	0.428	9.5%	2	21	6.8%	3	44	0.72	0.13 to 3.96	0.708	9.3%	20	215
Abdo. any	46.9%	23	49	29.5%	13	44	0.58	0.35 to 0.98	0.043	52.4%	11	21	29.5%	13	44	0.50	0.24 to 1.04	0.062	51.2%	110	215
Abdo. freq.	10.2%	5	49	6.8%	3	44	0.87	0.23 to 3.30	0.843	4.8%	1	21	6.8%	3	44	1.08	0.13 to 9.25	0.945	9.3%	20	215
Back any	46.9%	23	49	29.5%	13	44	0.70	0.42 to 1.16	0.162	47.6%	10	21	34.1%	15	44	0.79	0.45 to 1.40	0.423	54.0%	116	215
Back freq.	18.4%	9	49	9.1%	4	44	0.56	0.19 to 1.64	0.292	14.3%	3	21	9.1%	4	44	0.61	0.17 to 2.18	0.450	11.2%	24	215
Strain blad. any	40.8%	20	49	47.7%	21	44	1.15	0.74 to 1.77	0.533	33.3%	7	21	50.0%	22	44	1.35	0.71 to 2.54	0.361	42.8%	92	215
Strain blad. freq.	12.2%	6	49	18.2%	8	44	1.43	0.60 to 3.43	0.425	9.5%	2	21	4.5%	2	44	0.43	0.07 to 2.76	0.371	11.2%	24	215
Blad. not empty any	59.2%	29	49	63.6%	28	44	1.04	0.74 to 1.47	0.804	61.9%	13	21	65.9%	29	44	0.99	0.66 to 1.50	0.976	63.3%	136	215
Blad. not empty freq.	16.3%	8	49	18.2%	8	44	0.97	0.44 to 2.14	0.946	9.5%	2	21	11.4%	5	44	0.66	0.15 to 2.92	0.586	15.8%	34	215
Bowel not empty any	59.2%	29	49	63.6%	28	44	1.19	0.76 to 1.88	0.447	61.9%	13	21	65.9%	29	44	1.00	0.68 to 1.49	0.981	75.3%	162	215
Bowel not empty freq.	14.3%	7	49	13.6%	6	44	0.95	0.37 to 2.45	0.911	19.0%	4	21	18.2%	8	44	1.43	0.48 to 4.23	0.521	15.8%	34	215
Actions necessitated by prolapse symptoms																					
Fingers to ease discomfort	0.0%	0	45	0.0%	0	39	N/A	N/A	N/A	0.0%	0	20	2.6%	1	38	N/A	N/A	N/A	1.6%	3	185
Extra hygiene measures	4.5%	2	44	12.8%	5	39	2.28	0.48 to 10.85	0.302	5.3%	1	19	8.1%	3	37	1.40	0.15 to 13.10	0.766	7.5%	14	186

continued

TABLE 60 Individual prolapse symptoms at 6 months, 1 year and 2 years: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Fingers to help empty bladder	0.0%	0	46	0.0%	0	39	N/A	N/A	N/A	0.0%	0	21	0.0%	0	41	N/A	N/A	N/A	0.5%	1	186
Fingers to help empty bowel	2.2%	1	46	2.6%	1	39	1.18	0.08 to 18.24	0.906	4.8%	1	21	0.0%	0	39	N/A	N/A	N/A	3.3%	6	184
Digital evacuation of bowel	4.3%	2	46	7.7%	3	39	2.16	0.39 to 11.81	0.376	4.8%	1	21	4.9%	2	41	0.94	0.09 to 10.24	0.961	5.8%	11	189
2-year outcomes																					
Number of women at 2 years	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		
Individual prolapse symptoms																					
SCD any	30.2%	13	43	25.6%	10	39	0.78	0.38 to 1.60	0.497	25.0%	5	20	35.9%	14	39	1.17	0.47 to 2.87	0.739	43.4%	82	189
SCD freq.	7.0%	3	43	5.1%	2	39	0.84	0.15 to 4.74	0.845	5.0%	1	20	7.7%	3	39	1.10	0.10 to 12.20	0.941	16.4%	31	189
Pain any	25.6%	11	43	17.9%	7	39	0.70	0.31 to 1.56	0.382	30.0%	6	20	30.8%	12	39	0.77	0.34 to 1.76	0.539	41.3%	78	189
Pain freq.	4.7%	2	43	2.6%	1	39	0.55	0.05 to 5.84	0.621	5.0%	1	20	7.7%	3	39	0.56	0.05 to 6.71	0.646	9.5%	18	189
Abdo. any	23.3%	10	43	28.2%	11	39	1.16	0.54 to 2.52	0.702	20.0%	4	20	33.3%	13	39	1.34	0.55 to 3.27	0.526	45.0%	85	189
Abdo. freq.	2.3%	1	43	5.1%	2	39	2.84	0.27 to 29.91	0.384	5.0%	1	20	5.1%	2	39	0.86	0.08 to 9.20	0.901	10.1%	19	189
Back any	41.9%	18	43	30.8%	12	39	0.71	0.38 to 1.31	0.272	35.0%	7	20	33.3%	13	39	1.04	0.51 to 2.14	0.911	49.2%	93	189
Back freq.	9.3%	4	43	10.3%	4	39	0.83	0.20 to 3.53	0.806	5.0%	1	20	5.1%	2	39	1.52	0.14 to 16.13	0.729	12.2%	23	189
Strain blad. any	34.9%	15	43	53.8%	21	39	1.59	0.93 to 2.71	0.093	30.0%	6	20	41.0%	16	39	1.51	0.73 to 3.13	0.270	44.4%	84	189
Strain blad. freq.	9.3%	4	43	12.8%	5	39	1.34	0.48 to 3.70	0.575	0.0%	0	20	5.1%	2	39	N/A	N/A	N/A	13.2%	25	189
Blad. not empty any	55.8%	24	43	59.0%	23	39	1.30	0.90 to 1.87	0.158	65.0%	13	20	56.4%	22	39	0.86	0.57 to 1.30	0.467	63.5%	120	189
Blad. not empty freq.	9.3%	4	43	17.9%	7	39	1.82	0.59 to 5.62	0.299	0.0%	0	20	15.4%	6	39	N/A	N/A	N/A	19.0%	36	189
Bowel not empty any	55.8%	24	43	66.7%	26	39	1.12	0.76 to 1.64	0.579	45.0%	9	20	64.1%	25	39	1.60	0.84 to 3.03	0.152	72.0%	136	189
Bowel not empty freq.	7.0%	3	43	17.9%	7	39	2.07	0.67 to 6.45	0.208	5.0%	1	20	15.4%	6	39	2.81	0.41 to 19.20	0.292	19.0%	36	189

Symptom	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Actions necessitated by prolapse symptoms																					
Fingers to ease discomfort	0.0%	0	43	0.0%	0	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	38	N/A	N/A	N/A	1.1%	2	182
Extra hygiene measures	4.7%	2	43	10.3%	4	39	2.44	0.46 to 13.09	0.297	5.0%	1	20	5.3%	2	38	1.09	0.11 to 10.88	0.944	9.9%	18	182
Fingers to help empty bladder	0.0%	0	43	0.0%	0	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	39	N/A	N/A	N/A	0.5%	1	186
Fingers to help empty bowel	0.0%	0	43	2.6%	1	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	37	N/A	N/A	N/A	3.2%	6	187
Digital evacuation of bowel	0.0%	0	42	5.1%	2	39	N/A	N/A	N/A	0.0%	0	19	0.0%	0	39	N/A	N/A	N/A	7.0%	13	187

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Individual prolapse symptoms

Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time.; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely? (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad.* any: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.

Actions necessitated by prolapse symptoms

Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

TABLE 61 EuroQol-5 Dimensions (3-level version) at 6 months, 1 year and 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh						Trial 4: standard repair vs. mesh kit						
EQ-5D-3L	Standard		Synthetic		Effect size	95% CI	*p*-value	Standard		Mesh kit		Effect size	95% CI	*p*-value	CC2	
At 6 months																
Number of women	*N* = 50		*N* = 47					*N* = 22		*N* = 43					*N* = 214	
Score	0.77	(0.31) 48	0.83	(0.21) 46	0.00	–0.09 to 0.10	0.938	0.85	(0.23) 22	0.77	(0.26) 42	–0.04	–0.17 to 0.10	0.590	0.74	(0.26) 203
At 1 year																
Number of women	*N* = 49		*N* = 44					*N* = 21		*N* = 44					*N* = 216	
Score	0.74	(0.30) 50	0.83	(0.22) 43	0.03	–0.07 to 0.14	0.519	0.79	(0.27) 22	0.83	(0.19) 41	0.05	–0.07 to 0.17	0.411	0.73	(0.28) 209
At 2 years																
Number of women	*N* = 43		*N* = 39					*N* = 20		*N* = 39					*N* = 191	
Score	0.76	(0.29) 42	0.82	(0.19) 38	0.00	–0.11 to 0.11	0.975	0.76	(0.29) 20	0.87	(0.14) 38	0.13	0.02 to 0.25	0.025	0.75	(0.27) 188

Continuous variables are presented as 'mean (SD) *N*'.

TABLE 62 Urinary symptoms at 1 year and 2 years: Secondary trial

Symptom	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
1-year outcomes																					
Number of women at 1 year	*N* = 46			*N* = 39						*N* = 21			*N* = 41						*N* = 191		
Any incontinence	69.6%	32	46	64.1%	25	39	0.90	0.63 to 1.28	0.566	57.1%	12	21	73.2%	30	41	1.21	0.83 to 1.79	0.322	72.1%	137	190
ICIQ-UI-SF score	4.2	(3.9)	46	4.8	(5.1)	39	0.27	−1.55 to 2.09	0.768	3.3	(3.6)	21	5.4	(5.0)	40	0.55	−1.45 to 2.55	0.580	5.7	(5.1)	188
Severe incontinence	2.2%	1	46	12.8%	5	39	5.52	0.68 to 44.77	0.110	0.0%	0	21	10.0%	4	40	N/A	N/A	N/A	11.2%	21	188
UI QoL score	1.7	(2.4)	46	2.4	(3.2)	38	0.36	−0.81 to 1.53	0.533	1.2	(2.1)	21	2.2	(2.7)	41	0.30	−1.09 to 1.68	0.664	2.4	(2.9)	186
Stress UI	10.8%	4	37	9.7%	4	31	0.89	0.24 to 3.38	0.868	5.9%	1	17	17.1%	6	35	2.76	0.36 to 21.35	0.331	12.5%	20	160
Urgency UI	0.0%	0	46	5.3%	2	38	N/A	N/A	N/A	0.0%	0	21	7.3%	3	41	N/A	N/A	N/A	6.3%	12	189
Overactive bladder	0.0%	0	45	2.6%	1	38	N/A	N/A	N/A	0.0%	0	21	0.0%	0	41	N/A	N/A	N/A	3.7%	7	189
ICIQ-FLUTS filling score	3.7	(2.4)	45	4	(2.7)	38	0.41	−0.55 to 1.37	0.392	3.9	(3.0)	21	4.1	(2.0)	41	−0.09	−1.32 to 1.15	0.886	4.6	(2.9)	188
ICIQ-FLUTS voiding score	2.2	(2.3)	46	2.3	(2.1)	39	0.15	−0.76 to 1.06	0.744	2.0	(2.3)	21	2.1	(2.2)	41	−0.06	−1.23 to 1.11	0.916	2.2	(2.4)	188
ICIQ-FLUTS incontinence	3.9	(3.0)	37	4.5	(3.8)	31	0.22	−1.37 to 1.81	0.779	3.2	(3.0)	17	5.6	(4.5)	34	0.58	−1.47 to 2.63	0.562	5.2	(3.9)	153
2-year outcomes																					
Number of women at 2 years	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		
Any incontinence	60.5%	26	43	71.8%	28	39	1.10	0.75 to 1.59	0.634	65.0%	13	20	79.5%	31	39	1.18	0.87 to 1.59	0.292	71.2%	136	191
ICIQ-UI-SF score	3.8	(4.4)	42	5.0	(4.5)	39	1.04	−0.79 to 2.86	0.258	3.7	(3.7)	20	5.5	(5.1)	39	0.58	−1.52 to 2.68	0.574	5.5	(4.9)	189
Severe incontinence	7.1%	3	42	10.3%	4	39	1.64	0.38 to 7.07	0.507	5.0%	1	20	10.3%	4	39	1.58	0.20 to 12.48	0.663	12.2%	23	189
UI QoL score	1.3	(2.2)	40	2.1	(2.7)	39	0.60	−0.51 to 1.70	0.282	1.1	(1.8)	19	2.2	(3.1)	39	0.32	−1.00 to 1.65	0.619	2.3	(2.7)	184
Stress UI	13.9%	5	36	11.8%	4	34	1.35	0.40 to 4.55	0.626	11.8%	2	17	10.8%	4	37	0.86	0.21 to 3.54	0.833	16.4%	27	165

continued

TABLE 62 Urinary symptoms at 1 year and 2 years: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Urgency UI	4.7%	2	43	7.7%	3	39	1.34	0.24 to 7.46	0.734	5.0%	1	20	10.3%	4	39	1.71	0.21 to 13.74	0.613	8.4%	16	190
Overactive bladder	0.0%	0	43	5.1%	2	39	N/A	N/A	N/A	0.0%	0	20	2.6%	1	39	N/A	N/A	N/A	1.1%	2	189
ICIQ-FLUTS filling score	3.9	(2.3)	43	4.2	(3.1)	39	0.35	–0.64 to 1.34	0.483	4.1	(2.3)	20	4.1	(2.4)	39	–0.30	–1.64 to 1.03	0.644	4.5	(2.5)	185
ICIQ-FLUTS voiding score	1.6	(2.7)	42	2.3	(2.2)	39	0.54	–0.41 to 1.50	0.260	1.1	(1.3)	19	2.2	(2.1)	39	1.09	0.03 to 2.15	0.044	2.3	(2.3)	189
ICIQ-FLUTS incontinence	4.0	(3.5)	36	4.2	(3.9)	33	0.07	–1.56 to 1.70	0.934	3.6	(2.9)	17	4.7	(4.1)	37	0.30	–1.38 to 1.98	0.714	5.3	(4.1)	163

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

However, there was no difference between the randomised groups in either trial 3 or trial 4 with respect to any of the urinary outcomes measured.

The findings were virtually unchanged at 2 years (see *Table 62*): there did not appear to be any further recovery or deterioration in urinary symptoms over that time span. The benefits of surgery, and the lack of power to differentiate between the randomised groups in either trial 3 or trial 4, were largely maintained at 2 years. The results for the cohort women were similar.

Bowel symptoms

Detailed information on bowel symptoms was obtained at baseline, 1 year and 2 years (see *Tables 52* and *63*). Bowel frequency and constipation were largely unchanged after prolapse surgery. However, fewer women had bowel urgency or FI, and the effect of bowel symptoms on QoL was less than before surgery (*Table 63*). Nevertheless, there was no difference between the randomised groups with respect to any of the bowel outcomes measured.

The benefits of surgery, were largely maintained at 2 years (see *Table 63*). The data from the cohort women were similar.

Vaginal and sexual symptoms

Detailed information on vaginal and sexual symptoms was obtained at baseline, 1 year and 2 years (see *Tables 53* and *64*). Both the mean vaginal symptom score and the QoL score decreased (improved) after prolapse surgery (*Table 64*). However, there was no difference between the randomised groups for these outcomes.

More women were sexually active after surgery, and many fewer cited prolapse symptoms as a reason for not having a sex life (see *Table 64*). This was reflected in a halving of the ICI Sexual Matters score, and an even greater reduction (improvement) in the sex life QoL score. Women in the synthetic mesh and mesh kit groups did have higher (worse) scores on each of the outcomes measured, but this did not reach statistical significance. In summary, there was no difference between the randomised groups with respect to any of the vaginal or sexual symptom outcomes measured (see *Table 64*) due to the small sample size resulting in a lack of power.

The benefits of surgery, and the lack of power to differentiate between the randomised groups, were largely maintained at 2 years (see *Table 64*). The data from the cohort women were similar.

Postoperative prolapse measurements in randomised women

A 1-year clinic review was offered to all randomised women and 83% attended. Objective measurement showed improvement in each of the three prolapse compartments. The proportion of women with the leading prolapse edge beyond the hymen (> 0 cm) reduced substantially (*Table 65*). There was no statistically significant difference between groups in the prolapse stage, based on POP-Q scores or clinician's estimates of stage (see *Table 65*) in trial 3 (RR 0.75, 95% CI 0.33 to 1.68; $p = 0.479$) or in terms of failure defined as 'leading edge of the prolapse at > 0 cm beyond the hymen on POP-Q' (RR 0.59, 95% CI 0.18 to 1.92; $p = 0.380$).

There was statistical evidence of a difference between groups in trial 4: women who had a standard repair were more likely to have residual prolapse than those who were randomised to mesh kit (RR 0.24, 95% CI 0.07 to 0.83; $p = 0.024$; see *Table 65*). This may have been a chance finding as a result of the small sample size. Using the strict definition of failure of 'leading edge of the prolapse at > 0 cm beyond the hymen on POP-Q', 3 of 18 (16.7%) of the women who had undergone standard repair had residual prolapse compared with none of 35 women after receiving mesh kit treatment in trial 4.

TABLE 63 Bowel symptoms at 1 year and 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
1-year outcomes																					
Number of women at 1 year	*N* = 46			*N* = 39						*N* = 21			*N* = 41						*N* = 191		
Bowel frequency																					
> 3 daily	2.2%	1	45	5.1%	2	39	0.76	0.31 to 1.88	0.558	4.8%	1	21	4.9%	2	41	0.51	0.16 to 1.62	0.255	3.2%	6	188
1–3 times daily	37.8%	17	45	30.8%	12	39				28.6%	6	21	24.4%	10	41				33.5%	63	188
Once daily	35.6%	16	45	35.9%	14	39				42.9%	9	21	48.8%	20	41				45.2%	85	188
Every 2–3 days	20.0%	9	45	23.1%	9	39				19.0%	4	21	17.1%	7	41				14.9%	28	188
Weekly or less	4.4%	2	45	5.1%	2	39				4.8%	1	21	4.9%	2	41				3.2%	6	188
Constipation	8.9%	4	45	23.1%	9	39	1.48	0.54 to 4.06	0.443	4.8%	1	21	12.2%	5	41	2.74	0.35 to 21.74	0.339	17.4%	32	184
Bowel urgency	8.7%	4	46	2.6%	1	39	0.32	0.04 to 2.68	0.292	0.0%	0	21	2.5%	1	40	N/A	N/A	N/A	6.3%	12	190
FI (any)	26.1%	12	46	43.6%	17	39	1.41	0.84 to 2.35	0.190	28.6%	6	21	39.0%	16	41	1.59	0.57 to 4.49	0.378	36.0%	68	189
Passive FI	75.0%	9	12	94.1%	16	17				100.0%	6	6	93.8%	15	16				85.3%	58	68
Active FI	25.0%	3	12	5.9%	1	17				0.0%	0	6	6.3%	1	16				14.7%	10	68
Severe FI	10.9%	5	46	17.9%	7	39	1.38	0.48 to 3.97	0.545	9.5%	2	21	12.2%	5	41	1.36	0.30 to 6.17	0.690	8.5%	16	189
Bowel symptoms QoL	1.3	(2.1)	46	1.9	(2.3)	37	0.05	–0.83 to 0.94	0.903	1.0	(1.5)	20	2.1	(2.6)	41	0.23	–1.19 to 1.65	0.741	2.4	(2.7)	188
2-year outcomes																					
Number of women at 2 years	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		
Bowel frequency																					
> 3 daily	4.7%	2	43	5.1%	2	39	0.97	0.38 to 2.48	0.957	5.0%	1	20	5.1%	2	39	1.06	0.33 to 3.47	0.919	3.7%	7	191
1–3 times daily	32.6%	14	43	35.9%	14	39				35.0%	7	20	20.5%	8	39				36.6%	70	191
Once daily	44.2%	19	43	33.3%	13	39				50.0%	10	20	46.2%	18	39				42.4%	81	191
Every 2–3 days	16.3%	7	43	20.5%	8	39				10.0%	2	20	25.6%	10	39				14.7%	28	191
Weekly or less	2.3%	1	43	5.1%	2	39				0.0%	0	20	2.6%	1	39				2.6%	5	191

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit											
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Constipation	9.5%	4	42	10.5%	4	38	0.99	0.27 to 3.62	0.984	10.5%	2	19	12.8%	5	39	0.60	0.10 to 3.64	0.579	18.9%	36	190
Bowel urgency	7.0%	3	43	13.2%	5	38	1.73	0.45 to 6.71	0.425	5.0%	1	20	7.7%	3	39	1.50	0.17 to 13.44	0.718	7.4%	14	189
FI (any)	27.9%	12	43	44.7%	17	38	1.35	0.74 to 2.47	0.326	30.0%	6	20	38.5%	15	39	1.04	0.47 to 2.31	0.918	37.0%	70	189
Passive FI	83.3%	10	12	70.6%	12	17				83.3%	5	6	80.0%	12	15				82.9%	58	70
Active FI	16.7%	2	12	29.4%	5	17				16.7%	1	6	20.0%	3	15				17.1%	12	70
Severe FI	4.7%	2	43	15.8%	6	38	2.04	0.43 to 9.66	0.371	10.0%	2	20	15.4%	6	39	1.92	0.43 to 8.52	0.391	13.2%	25	189
Bowel symptoms QoL	1.5	(2.3)	42	2.0	(2.7)	38	–0.30	–1.24 to 0.65	0.525	2.0	(3.0)	20	2.3	(2.7)	37	–0.67	–2.26 to 0.93	0.398	2.6	(2.8)	186

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: Any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 64 Vaginal and sexual symptoms at 1 year and 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									Cohort		
Symptom	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
1-year outcomes																					
Number of women	*N* = 46			*N* = 39						*N* = 21			*N* = 41						*N* = 191		
Vaginal symptoms																					
ICIQ-VS	8.3	(7.4)	44	7.9	(8.6)	37	–1.29	–4.99 to 2.42	0.487	6.7	(6.0)	18	5.8	(4.8)	35	–2.82	–6.67 to 1.02	0.143	10.1	(9.2)	171
Vaginal symptoms QoL score	1.9	(2.8)	42	2.0	(2.8)	38	–0.11	–1.43 to 1.22	0.873	0.6	(0.8)	18	1.8	(2.3)	36	0.97	–0.25 to 2.18	0.113	2.2	(2.9)	179
Vagina too tight	7.0%	3	43	2.7%	1	37	0.38	0.04 to 3.46	0.390	0.0%	0	20	5.3%	2	38	N/A	N/A	N/A	6.4%	11	172
Sexual symptoms																					
Sex life at present	40.0%	18	45	48.8%	20	41				28.6%	6	21	41.0%	16	39				35.3%	65	184
Reason for no sex life																					
No partner	37.0%	10	27	28.6%	6	21				40.0%	6	15	30.4%	7	23				37.0%	44	119
Vaginal symptoms	11.1%	3	27	9.5%	2	21				13.3%	2	15	4.3%	1	23				10.1%	12	119
Prolapse symptoms	3.7%	1	27	23.8%	5	21				0.0%	0	15	8.7%	2	23				21.0%	25	119
Other reason	40.7%	11	27	28.6%	6	21				33.3%	5	15	56.5%	13	23				28.6%	34	119
Reason not given	7.4%	2	27	9.5%	2	21				13.3%	2	15	0.0%	0	23				3.4%	4	
Dyspareunia	0.0%	0	18	13.0%	3	23	N/A	N/A	N/A	0.0%	0	6	5.6%	1	18	N/A	N/A	N/A	11.8%	9	76
ICI Sexual Matters score	5.4	(9.3)	18	14.3	(15.4)	21	5.10	–5.79 to 16.00	0.295	4.0	(6.7)	6	16.9	(15.5)	18	6.58	–14.62 to 27.77	0.314	15.7	(16.7)	73
Sex life QoL score	2.3	(3.1)	19	3.5	(3.5)	22	0.37	–1.92 to 2.67	0.721	0.3	(0.8)	6	3.7	(3.5)	18	3.74	–6.46 to 13.93	0.256	4.2	(4.0)	76
2-year outcomes																					
Number of women	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		

Symptom	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									Cohort		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Vaginal symptoms																					
ICIQ-VS	7.3	(7.6)	39	7.9	(7.8)	37	–0.64	–4.56 to 3.28	0.742	6.1	(6.2)	17	7.9	(7.4)	36	0.08	–4.91 to 5.08	0.973	10.5	(9.3)	169
Vaginal symptoms QoL score	1.8	(2.8)	40	1.8	(2.4)	39	–0.14	–1.40 to 1.12	0.824	1.4	(3.2)	18	1.8	(2.5)	35	–0.16	–2.09 to 1.76	0.864	2.6	(3.0)	181
Vagina too tight	4.9%	2	41	7.9%	3	38	1.71	0.30 to 9.59	0.543	0.0%	0	18	2.7%	1	37	N/A	N/A	N/A	5.2%	9	174
Sexual symptoms																					
Sex life at present	32.6%	14	43	55.3%	21	38				30.0%	6	20	39.5%	15	38				34.6%	63	182
Reason for no sex life																					
No partner	34.5%	10	29	23.5%	4	17				42.9%	6	14	21.7%	5	23				31.9%	38	119
Vaginal symptoms	13.8%	4	29	5.9%	1	17				0.0%	0	14	8.7%	2	23				7.6%	9	119
Prolapse symptoms	3.4%	1	29	17.6%	3	17				0.0%	0	14	8.7%	2	23				12.6%	15	119
Other reason	34.5%	10	29	35.3%	6	17				42.9%	6	14	52.2%	12	23				38.7%	46	119
Reason not given	13.8%	4	29	17.6%	3	17				14.3%	2	14	8.7%	2	23				9.2%	11	119
Dyspareunia	0.0%	0	15	4.5%	1	22	N/A	N/A	N/A	0.0%	0	6	0.0%	0	16	N/A	N/A	N/A	10.0%	7	70
ICI Sexual Matters score	8.5	(10.8)	15	13.9	(14.0)	22	6.57	–5.47 to 18.62	0.255	2.7	(4.1)	6	12.2	(9.8)	16	5.64	–91.28 to 102.56	0.595	18.1	(16.3)	70
Sex life QoL score	2.5	(3.5)	15	3.7	(3.6)	23	1.49	–1.68 to 4.67	0.320	1.5	(3.2)	6	2.8	(2.8)	17	2.33	–32.13 to 36.78	0.549	4.4	(3.8)	73

N/A, not applicable.

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

TABLE 65 Objective measures of prolapse at 1-year clinic review: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit								
POP-Q measurement/stage	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value
1-year reviews	*N* = 46			*N* = 44						*N* = 21			*N* = 38					
POP-Q measurement (cm)																		
Ba (posterior edge)	–1.4	(1.5)	42	–1.4	(1.4)	41	–0.22	–0.80 to 0.36	0.445	–1.2	(1.9)	19	–1.8	(1.0)	35	–0.74	–1.4 to –0.10	0.026
C (cervix/vault)	–5.6	(2.4)	41	–6.2	(1.5)	41	–0.61	–1.38 to 0.16	0.119	–5.1	(2.7)	18	–6.0	(1.8)	33	–0.65	–1.6 to 0.3	0.173
Bp (posterior edge)	–1.8	(1.6)	41	–2.2	(1.1)	41	–0.49	–1.08 to 0.10	0.099	–1.9	(1.7)	18	–2.2	(0.8)	34	–0.38	–1.2 to 0.4	0.317
TVL	7.7	(1.2)	43	7.9	(1.4)	42	0.09	–0.47 to 0.65	0.746	7.7	(1.0)	19	8.1	(1.2)	33	0.64	0.1 to 1.20	0.028
Overall POP-Q stage																		
0	13.6%	6	44	7.0%	3	43	0.75	0.33 to 1.68	0.479	10.5%	2	19	14.3%	5	35	0.24	0.07 to 0.83	0.024
1	36.4%	16	44	44.2%	19	43				31.6%	6	19	45.7%	16	35			
2	40.9%	18	44	46.5%	20	43				42.1%	8	19	40.0%	14	35			
3	9.1%	4	44	2.3%	1	43				15.8%	3	19	0.0%	0	35			
4	0.0%	0	44	0.0%	0	43				0.0%	0	19	0.0%	0	35			
2b, 3 or 4	*14.0%*	*6*	*43*	*14.0%*	*6*	*43*	*0.59*	*0.18 to 1.92*	*0.380*	*16.7%*	*3*	*18*	*0.0%*	*0*	*35*	*N/A*	*N/A*	*N/A*

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

Further treatment required for failure or adverse effects at 6 months, 1 year and 2 years

When women reported at 6 months or later that they had been readmitted to hospital, we verified the information by enquiry from site staff when necessary and corrected the information where necessary. A hospital readmission was automatically counted as a SAE if it was related to the initial prolapse surgery. Readmission for related adverse effects such as bleeding or infection was differentiated from (a) new surgery for pelvic organ prolapse (repeat if same compartment, further if in the opposite compartment); (b) readmission for continence surgery; and (c) readmission for surgical mesh removal.

Readmission for adverse effects

The overall rate of readmission was low, and there was no significant difference between the randomised groups. The rate in the first 6 months, ranging from 0% to 6.4% (*Table 66*) was mostly related to adverse effects (two cases of infection in the standard arm, one case each of retention, constipation and adhesions in the mesh inlay arm), whereas after that time only one woman was readmitted (randomised to mesh inlay, for a Fenton's operation for vaginal tightness). There were no statistically significant differences between the randomised groups at 1 year or 2 years (see *Table 66*).

Readmission for new prolapse surgery

Four women reported that they had had new prolapse surgery in the first year and a further eight in the second year (at least one woman in each of the randomised groups), with one woman having surgery in both years. The numbers were too few to draw conclusions (see *Table 66*). Complete questionnaire data were received from 122 randomised women and 185 cohort women. The repeat prolapse surgery rate was therefore 10 of 122 (8.2%) for the randomised women and 17 of 185 (9.2%) in the cohort (see *Table 66*).

Readmission for continence surgery

Only three randomised women had continence surgery in the first year, and another three in the second year (see *Table 66*). The numbers were too few to differentiate between the groups. The surgery rate was 5 of 122 (4.1%) for the randomised women. In the cohort, three women had continence surgery in the first year, and four in the second year, with one woman having continence surgery in both years. The surgery rate was 6 of 186 (3.2%) in the cohort.

Treatment for mesh complications in the Secondary trials

In the first year, none of the women in the standard group and 6/52 (11.5%) in the mesh inlay group had a mesh complication (see *Table 66*). There were a further 3 of 46 (6.5%) mesh complications in the mesh kit group. Three women in the mesh inlay group had surgery to remove or overlay the mesh, and one in the mesh kit group. In the second year, none of the women in the standard group and 2/52 (3.8%) in the mesh inlay group had a mesh complication, with a further 2 of 46 (4.3%) in the mesh kit group. Of these, only one of the women in the mesh inlay group and one in the mesh kit group required surgical correction of the mesh exposure.

So in total, six women required mesh surgery in the 2 years of follow-up. A further six women received conservative treatment (such as mesh trimming in outpatients, oestrogen treatment or cautery with silver nitrate) and the rest did not require any treatment (see *Table 66*).

The cumulative mesh complication rates over 2 years were 7 of 52 (13.5%) for mesh inlay and 4 of 46 (8.7%) for mesh kit, with no mesh exposures after standard repair.

Other treatment for prolapse symptoms

Few women required other treatment – such as pessaries or physiotherapy – for symptoms, and there was no difference between the randomised groups regarding further use of services (see also *Chapter 7*).

TABLE 66 Further treatment required within 2 years: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit												
Further treatment	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
6-month outcomes																						
Number of women at 6 months	*N* = 50			*N* = 47						*N* = 22			*N* = 43						*N* = 214		
Readmitted (0–6 months)	4.0%	2[a]	50	6.4%	3[b]	47	1.76	0.30 to 10.37	0.532	0.0%	0	22	0.0%	0	43	N/A	N/A	N/A	2.8%	6[c]	214
Readmitted (6–12 months)	0.0%	0	49	0.0%	0	44	N/A	N/A	N/A	0.0%	0	21	2.3%	1[d]	44	N/A	N/A	N/A	1.9%	4[e]	216
1-year outcomes																						
Number of women at 1 year	*N* = 49			*N* = 44						*N* = 21			*N* = 44						*N* = 216		
New prolapse surgery	6.1%	3	49	2.3%	1	44	0.37	0.04 to 3.43	0.382	9.5%	2	21	0.0%	0	44	N/A	N/A	N/A	5.1%	11	216
Same compartment	6.1%	3	49	0.0%	0	44	N/A	N/A	N/A	9.5%	2	21	0.0%	0	44	N/A	N/A	N/A	3.2%	7	216
Different compartment	0.0%	0	49	2.3%	1	44	N/A	N/A	N/A	0.0%	0	21	0.0%	0	44	N/A	N/A	N/A	1.9%	4	216
Waiting for prolapse surgery	2.0%	1	49	2.3%	1	44	1.06	0.07 to 16.23	0.967	0.0%	0	21	2.3%	1	44	N/A	N/A	N/A	0.9%	2	216
Continence surgery	0.0%	0	49	2.3%	1	44	N/A	N/A	N/A	0.0%	0	21	4.5%	2	44	N/A	N/A	N/A	1.4%	3	216
Waiting for continence surgery	0.0%	0	49	0.0%	0	44	N/A	N/A	N/A	0.0%	0	21	2.3%	1	44	N/A	N/A	N/A	1.9%	4	216
Stitches removed	6.4%	3	47	2.4%	1	42	0.34	0.04 to 3.03	0.331	5.0%	1	20	2.3%	1	43	0.48	0.03 to 7.14	0.596	3.8%	8	208
Any mesh complication	0.0%	0	55	11.5%	6	52				0.0%	0	25	6.5%	3	46				1. 6%	4	244
Surgical removal	0.0%	0	55	5.8%	3	52				0.0%	0	25	2. 2%	1	46				1.6%	4	244
Conservative treatment	0.0%	0	55	3.8%	2	52				0.0%	0	25	4.3%	2	46				0.0%	0	244
No treatment	0.0%	0	55	1.9%	1	52				0.0%	0	25	0.0%	0	46				0.0%	0	244
De novo mesh	0.0%	0	55	9.6%	5	52				0.0%	0	25	4.3%	2	46				0.8%	2	244
Concomitant, etc. mesh	0.0%	0	55	0.9%	1	52				0.0%	0	25	2.2%	1	46				0.8%	2	244

Further treatment	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									CC2		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
Treatment for prolapse at 1 year																					
Medicines for prolapse	21.3%	10	47	27.3%	12	44	1.49	0.71 to 3.12	0.292	23.8%	5	21	24.4%	10	41	1.11	0.43 to 2.85	0.826	21.6%	46	213
Oestrogens	26.5%	13	49	34.1%	15	44	1.34	0.72 to 2.46	0.355	19.0%	4	21	27.3%	12	44	1.43	0.52 to 3.92	0.485	21.3%	46	216
Ring pessary	0.0%	0	49	0.0%	0	44	N/A	N/A	N/A	0.0%	0	21	0.0%	0	44	N/A	N/A	N/A	3.7%	8	216
Shelf pessary	0.0%	0	49	0.0%	0	44	N/A	N/A	N/A	0.0%	0	21	0.0%	0	44	N/A	N/A	N/A	1.4%	3	216
Physiotherapy	8.5%	4	47	18.6%	8	43	2.20	0.71 to 6.77	0.169	5.0%	1	20	9.3%	4	43	2.25	0.27 to 18.63	0.454	10.6%	22	208
GP for prolapse	29.2%	14	48	36.4%	16	44	1.27	0.71 to 2.27	0.422	30.0%	6	20	22.5%	9	40	0.71	0.29 to 1.72	0.446	26.0%	53	204
Practice nurse	4.2%	2	48	14.0%	6	43	4.26	0.83 to 22.00	0.083	5.0%	1	20	0.0%	0	40	N/A	N/A	N/A	10.0%	20	200
GOPD	42.2%	19	45	29.5%	13	44	0.73	0.41 to 1.30	0.283	47.4%	9	19	40.5%	17	42	0.72	0.39 to 1.33	0.298	38.9%	81	208
Treatment for urinary problems at 1 year																					
Pads	36.7%	18	49	36.4%	16	44	0.89	0.53 to 1.50	0.658	30.0%	6	20	31.0%	13	42	0.88	0.38 to 2.04	0.767	40.3%	85	211
Permanent catheter	2.4%	1	42	0.0%	0	40	N/A	N/A	N/A	10.5%	2	19	0.0%	0	39	N/A	N/A	N/A	1.0%	2	200
Intermittent catheter	4.9%	2	41	0.0%	0	39	N/A	N/A	N/A	5.9%	1	17	2.6%	1	39	0.41	0.03 to 6.11	0.515	2.5%	5	202
Drugs for UI	12.2%	6	49	20.5%	9	44	1.90	0.75 to 4.86	0.178	9.5%	2	21	13.6%	6	44	1.45	0.32 to 6.45	0.628	13.9%	30	216
2-year outcomes																					
Number of women at 2 years	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		
Readmitted (12–24 months)	0.0%	0	43	2.6%	1[f]	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	39	N/A	N/A	N/A	1.6%	3[g]	191
New prolapse surgery	9.3%	4	43	7.7%	3	39	0.76	0.18 to 3.17	0.711	10.0%	2	20	2.6%	1	39	0.15	0.01 to 2.07	0.158	4.7%	9	191
Same compartment	7.0%	3	43	2.6%	1	39	0.35	0.04 to 3.21	0.353	5.0%	1	20	2.6%	1	39	0.55	0.04 to 8.36	0.665	3.7%	7	191
Different compartment	2.3%	1	43	5.1%	2	39	1.73	0.16 to 18.53	0.652	5.0%	1	20	0.0%	0	39	N/A	N/A	N/A	1.0%	2	191
Waiting for prolapse surgery	0.0%	0	43	2.6%	1	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	39	N/A	N/A	N/A	0.5%	14	191

continued

TABLE 66 Further treatment required within 2 years: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit												
Further treatment	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Continence surgery	0.0%	0	43	2.6%	1	39	N/A	N/A	N/A	0.0%	0	20	5.1%	2	39	N/A	N/A	N/A	2.1%	4	191
Waiting for continence surgery	0.0%	0	43	0.0%	0	39	N/A	N/A	N/A	0.0%	0	20	0.0%	0	39	N/A	N/A	N/A	0.0%	0	191
Stitches removed	0.0%	0	41	2.6%	1	39	N/A	N/A	N/A	0.0%	0	19	0.0%	0	38	N/A	N/A	N/A	2.2%	4	186
Any mesh complication	0.0%	0	55	3.8%	2	52				0.0%	0	25	4.3%	2	46				0.8%	2	244
Surgical removal	0.0%	0	55	1.9%	1	52				0.0%	0	25	2.2%	1	46				0.4%	1	244
Conservative	0.0%	0	55	1.9%	1	52				0.0%	0	25	2.2%	1	46				0.4%	1	244
No treatment	0.0%	0	55	0.0%	0	52				0.0%	0	25	0.0%	0	46				0.0%	0	244
De novo mesh	0.0%	0	55	1.9%	1	52				0.0%	0	25	4.3%	2	46				0.4%	1	244
Concomitant, etc. mesh	0.0%	0	55	1.9%	1	52				0.0%	0	25	0.0%	0	46				0.4%	1	244
Treatment for prolapse at 2 years																					
Medicines for prolapse	11.9%	5	42	17.9%	7	39	1.80	0.61 to 5.36	0.288	10.0%	2	20	7.7%	3	39	0.72	0.13 to 3.88	0.701	16.3%	31	190
Oestrogens	16.3%	7	43	28.2%	11	39	1.74	0.75 to 4.07	0.198	15.0%	3	20	23.1%	9	39	1.50	0.47 to 4.81	0.492	25.1%	48	191
Ring pessary	4.7%	2	43	2.6%	1	39	0.61	0.06 to 6.33	0.682	5.0%	1	20	2.6%	1	39	0.56	0.04 to 8.28	0.673	2.6%	5	191
Shelf pessary	7.0%	3	43	2.6%	1	39	0.41	0.05 to 3.66	0.424	5.0%	1	20	0.0%	0	39	N/A	N/A	N/A	3.1%	6	191
Physiotherapy	4.8%	2	42	10.3%	4	39	1.97	0.39 to 9.99	0.411	5.0%	1	20	5.1%	2	39	1.16	0.11 to 11.96	0.902	10.2%	19	187
GP for prolapse	9.5%	4	42	18.4%	7	38	1.72	0.55 to 5.40	0.355	15.8%	3	19	10.5%	4	38	0.77	0.20 to 3.00	0.704	18.2%	34	187
Practice nurse	9.3%	4	43	2.6%	1	38	0.26	0.03 to 2.19	0.214	15.0%	3	20	0.0%	0	39	N/A	N/A	N/A	4.9%	9	185
GOPD	23.3%	10	43	26.3%	10	38	1.08	0.51 to 2.31	0.834	15.0%	3	20	12.8%	5	39	0.84	0.23 to 3.07	0.791	21.3%	40	188

Further treatment	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit										CC2		
	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value			
Treatment for urinary problems at 2 years																						
Pads	27.9%	12	43	20.5%	8	39	0.67	0.30 to 1.48	0.320	15.0%	3	20	27.0%	10	37	1.57	0.48 to 5.10	0.455	41.2%	77	187
Permanent catheter	0.0%	0	42	0.0%	0	38	N/A	N/A	N/A	5.3%	1	19	0.0%	0	38	N/A	N/A	N/A	0.0%	0	188
Intermittent catheter	2.4%	1	42	0.0%	0	38	N/A	N/A	N/A	5.3%	1	19	2.6%	1	38	0.54	0.04 to 7.98	0.655	1.6%	3	187
Drugs for UI	14.0%	6	43	17.9%	7	39	1.28	0.45 to 3.61	0.644	5.0%	1	20	15.4%	6	39	3.34	0.44 to 25.41	0.243	13.1%	25	191

GOPD, Gynaecology Outpatients Department; N/A, not applicable.
a Reasons for readmission (standard; 0–6 months): infection (1), other (1).
b Reasons for readmission (synthetic; 0–6 months): retention (1), adhesions (1), constipation (1).
c Reasons for readmission (CC2; 0–6 months): bleeding (2), infection (2), pain (2).
d Reasons for readmission (mesh kit; 6–12 months): revision prolapse surgery (Fenton's test) (1).
e Reasons for readmission (CC2; 6–12 months): adhesions (3), other (1).
f Reasons for readmission (synthetic; 12–24 months): revision prolapse surgery (Fenton's) (1).
g Reasons for readmission (CC2; 12–24 months): adhesions (2), revision prolapse surgery (Fenton's test) (1).

Satisfaction with treatment at 1 year and 2 years

Women reported that they took around 3 months to resume normal activities (*Table 67*), with no differences between the randomised groups in trial 3, but in trial 4 the 19 women in the standard arm took significantly longer than those who were randomised to a mesh kit ($p = 0.011$). Over 80% of the randomised women reported that they were very much or much better than before surgery at 1 year, and similar proportions were completely or fairly satisfied. At 1 year, 89.7% of randomised women reported that they would 'recommend the surgery to a friend'. The data were similar at 1 year and 2 years (see *Table 67*), suggesting that, on average, the positive benefits of surgery were sustained, with no statistically significant differences between the groups in either trial. The results for the cohort women were similar (see *Table 67*).

These findings are in line with the clinical outcome data, supporting the positive and sustained benefits of prolapse surgery for the majority of women.

Discussion

Summary of findings

Effectiveness

There were no statistically significant differences at 1 year in the primary clinical or economic outcomes after prolapse surgery using native tissue, synthetic non-absorbable mesh or a mesh kit to reinforce the repair in either trial 3 or trial 4. However, because of the smaller numbers, these trials did not have enough statistical power to rule out any potentially true clinical differences. This was reflected in the wide CIs around the primary outcome – prolapse symptoms measured by the POP-SS at 1 year – of –0.41 (95% CI –2.92 to 2.11) in trial 3 and –1.21 (95% CI –4.13 to 1.72) in trial 4 (see *Table 59*). Although there were also no differences in the secondary clinical or objective outcomes, or in the proportion of women requiring further treatment in either of the trials, these analyses were not sufficiently powered to be conclusive.

Adverse effects

The overall incidence of serious adverse effects was around 10% (see *Table 66*), primarily pain, infection and urinary retention. Women could have a mesh-related complication only if they received mesh: the total numbers are very small. The cumulative mesh complication rates over 2 years were 7 of 52 (13.5%) for mesh inlay and 4 of 46 (8.7%) for mesh kit, with no mesh exposures after standard repair.

Cost-effectiveness

See *Chapter 7*.

Strengths and weaknesses

Strengths

As the women who were having a repeat repair were recruited opportunistically alongside the women who were having their first repair, the numbers were, as expected, too small to achieve statistical power for any of the outcomes. The numbers were reduced by our very strict definition of 'repeat repair', which required that the previous surgery had to be in the same compartment. About 10% of women who had previous surgery in the opposite compartment were therefore recruited into the Primary trial (see *Chapter 4*). In addition, women were less likely to be randomised than in the Primary trial (around 61% declined randomisation, further reducing the numbers).

The PROSPECT Study is rare in being one of the few RCTs to distinguish between primary and secondary surgery. Although the trial on its own was not sufficiently powered to detect a difference, this had two

TABLE 67 Satisfaction with surgery: Secondary trial

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									
Recovery/satisfaction'	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
1-year questionnaires	*N* = 46			*N* = 39						*N* = 21			*N* = 41						*N* = 191		
Time to recovery (months)	3.4	(2.4)	42	3.5	(2.2)	39	0.20	–0.77 to 1.16	0.681	4.5	(3.0)	19	2.9	(1.5)	34	–1.66	–2.91 to –0.41	0.011	3.2	(1.8)	170
Prolapse compared with before surgery																					
Very much better	51.2%	22	43	55.3%	21	38	1.18	0.47 to 2.95	0.731	61.1%	11	18	46.2%	18	35.4%	64	181	0.372	35.4%	64	181
Much better	25.6%	11	43	26.3%	10	38				16.7%	3	18	41.0%	16	33.7%	61	181		33.7%	61	181
A little better	18.6%	8	43	10.5%	4	38				16.7%	3	18	5.1%	2	13.3%	24	181		13.3%	24	181
No change	0.0%	0	43	7.9%	3	38				0.0%	0	18	0.0%	0	6.1%	11	181		6.1%	11	181
A little worse	0.0%	0	43	0.0%	0	38				0.0%	0	18	2.6%	1	6.1%	11	181		6.1%	11	181
Much worse	2.3%	1	43	0.0%	0	38				5.6%	1	18	2.6%	1	1.7%	3	181		1.7%	3	181
Very much worse	2.3%	1	43	0.0%	0	38				0.0%	0	18	2.6%	1	3.9%	7	181		3.9%	7	181
Satisfaction with surgery																					
Completely satisfied	45.5%	20	44	41.0%	16	39	0.82	0.31 to 2.16	0.685	52.6%	10	19	43.6%	17	35.4%	64	181	0.534	35.4%	64	181
Fairly satisfied	38.6%	17	44	35.9%	14	39				36.8%	7	19	33.3%	13	43.1%	78	181		43.1%	78	181
Fairly dissatisfied	9.1%	4	44	7.7%	3	39				5.3%	1	19	10.3%	4	7.2%	13	181		7.2%	13	181
Very dissatisfied	2.3%	1	44	2.6%	1	39				0.0%	0	19	2.6%	1	9.4%	17	181		9.4%	17	181
Not sure	4.5%	2	44	12.8%	5	39				5.3%	1	19	10.3%	4	5.0%	9	181		5.0%	9	181
Recommend to a friend	90.5%	38	42	86.5%	32	37	0.95	0.81 to 1.12	0.575	94.4%	17	18	91.9%	34	83.8%	145	173	0.653	83.8%	145	173
2-year questionnaires	*N* = 43			*N* = 39						*N* = 20			*N* = 39						*N* = 191		

continued

TABLE 67 Satisfaction with surgery: Secondary trial (*continued*)

	Trial 3: standard repair vs. synthetic mesh									Trial 4: standard repair vs. mesh kit									
Recovery/satisfaction'	Standard			Synthetic			Effect size	95% CI	*p*-value	Standard			Mesh kit			Effect size	95% CI	*p*-value	CC2		
Prolapse compared with before surgery																					
Very much better	47.6%	20	42	48.7%	19	39	1.01	0.41 to 2.49	0.974	45.0%	9	20	50.0%	19	38	1.53	0.47 to 4.96	0.478	37.4%	70	187
Much better	33.3%	14	42	25.6%	10	39				40.0%	8	20	39.5%	15	38				28.3%	53	187
A little better	9.5%	4	42	10.3%	4	39				0.0%	0	20	5.3%	2	38				17.6%	33	187
No change	4.8%	2	42	12.8%	5	39				5.0%	1	20	0.0%	0	38				6.4%	12	187
A little worse	2.4%	1	42	2.6%	1	39				5.0%	1	20	2.6%	1	38				3.7%	7	187
Much worse	2.4%	1	42	0.0%	0	39				5.0%	1	20	0.0%	0	38				4.8%	9	187
Very much worse	0.0%	0	42	0.0%	0	39				0.0%	0	20	2.6%	1	38				1.6%	3	187
Satisfaction with surgery																					
Completely satisfied	50.0%	20	40	48.7%	19	39	0.96	0.37 to 2.49	0.935	38.9%	7	18	52.6%	20	38	1.87	0.56 to 6.24	0.309	38.9%	72	185
Fairly satisfied	37.5%	15	40	35.9%	14	39				55.6%	10	18	36.8%	14	38				34.6%	64	185
Fairly dissatisfied	2.5%	1	40	2.6%	1	39				0.0%	0	18	2.6%	1	38				13.5%	25	185
Very dissatisfied	2.5%	1	40	7.7%	3	39				5.6%	1	18	2.6%	1	38				9.7%	18	185
Not sure	7.5%	3	40	5.1%	2	39				0.0%	0	18	5.3%	2	38				3.2%	6	185
Recommend to a friend	97.5%	39	40	82.1%	32	39	0.83	0.65 to 1.06	0.00	100.0%	18	18	97.2%	35	36	N/A	N/A	N/A	81.6%	142	174

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Satisfaction with surgery
How is prolapse compared with before surgery? Very much better = cured [1]; much or a little better (or very much better) = improved or cured [< 4]; no change or worse = failed [> 3].
Satisfied with results of operation? Completely satisfied = cured [1]; fairly satisfied = improved or cured [1 or 2]; fairly or very dissatisfied = failed [3 or 4]; not sure = separate category [5].

important implications. First, the information is now available for meta-analysis with other trials if women who were having a further repair are reported separately. If this happens, a meta-analysis in the future will shed more light on the fate of women whose surgery has already failed. It has therefore set a marker to all future trials (and indeed past ones) that prolapse surgery trials should be reported using the subgroups of primary and secondary surgery (defined as repeat in the same compartment). Second, it has made the clinical community more aware of the distinction, both in the presentation of their patients and that different treatment might be appropriate for these women.

Another one of the strengths of the Secondary trial was its pragmatic reflection of actual practice in a representative sample of UK prolapse surgeons across a large number of hospital settings. This was reflected in the range of concomitant surgery, and our ability to differentiate between women who were having a first or a repeat procedure in a particular compartment. Owing to preference or local resources available, surgeons were not all able to randomise between all three options but the analysis by strata took account of this.

Non-randomised cohort

Another strength was the inclusion of women who were not randomised. Data collection using the same questionnaires as for the randomised (trial) women demonstrated that our population was representative of the majority of women who were having prolapse surgery in the UK (see *Chapter 3*). Outcome data collected from those cohort women demonstrated that their outcomes were similar to those from the randomised women, thus ensuring generalisability of the findings. A further benefit was the ability to identify rare adverse effects.

Pragmatic nature of the research

Our secure and effective randomisation programme ensured that women were comparable at baseline and that concomitant surgery and other confounding variables were accounted for.

Validated outcome measures

We used validated outcome measures – such as the Pelvic Organ Prolapse Symptom scale and ICI-Q suite of instruments – to measure women's symptoms of pelvic floor dysfunction, ensuring that our findings are comparable with other trials and can be combined in meta-analysis. We captured a wide range of adverse effects and made efforts to verify these from alternative sources when possible. Essential missing data were actively sought from the women. Participants, outcome assessors and data entry clerks were blinded to randomisation and, as far as possible, to treatment actually received.

Weaknesses

Limitations of our study should be acknowledged. The large number of interventions and outcomes make it likely that some differences may have occurred by chance. Furthermore, the smaller numbers in the Secondary trial meant that we would have been able to identify only large differences, which we did not find.

The number of women randomised to the secondary RCT was small. The trial was not designed so that a prespecified level of power should be achieved (unlike the primary RCT). Further to this, there were fewer recruits to the Secondary trial than had been anticipated as a result of our stricter definition of a secondary repair.

Because of the chronic and relapsing nature of prolapse, longer follow-up is required: the average time to a repeat operation is around 12 years.[4] Although we did not identify differences in the repeat surgery rate between the groups, it is likely that 2 years is too short a time scale to provide a definitive answer. We have commenced follow-up of the PROSPECT women for at least 6 years after surgery, and also plan electronic data linkage to capture outcomes from non-responders.

The POP-Q system classes measurements from –1 cm inside the hymen to 1 cm as stage 2. We and other researchers[28] have arbitrarily used a measurement of > 0 cm to indicate objective failure, while recognising that women with worse findings may not have symptoms and vice versa (women with objective 'cure' may still have prolapse symptoms). However, *Table 65* shows that the findings would have been the same whichever stage of prolapse was chosen as the cut-off.

Conclusions

The information from the Secondary trial has been inconclusive either in terms of symptoms or anatomical cure from the use of synthetic mesh or a mesh kit in women who were having repeat prolapse surgery. We encourage existing and future triallists to report results for primary and repeat prolapse surgery separately, so that more information can be identified for this group of women who are at even higher risk of failure than after their first repair.[4]

We are unable to say whether or not mesh or a mesh kit confers benefit to women who were having a repeat prolapse repair, in terms of prolapse symptoms or anatomical cure of prolapse in the first 2 years after surgery. However, some women required an additional surgical procedure to remove exposed mesh, which may be considered to be an unnecessary risk. Long-term follow-up may show whether or not the excess risk is compensated for by a decreased need for repeat surgery in the future.

Chapter 7 Health economics results: Secondary trial

This chapter describes the results of the within-trial cost–utility analysis over 2 years of follow-up for women who were having a secondary prolapse surgical procedure. These are the results pertaining to women randomised to RCT2A (three-way comparison of mesh kits vs. mesh inlay vs. standard repair) and RCT2B (comparisons of mesh inlay vs. standard repair).

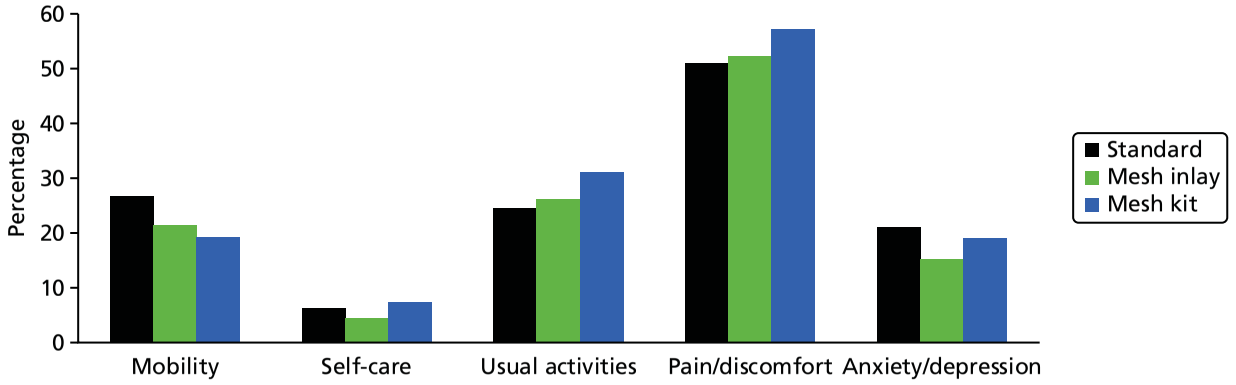
For the purposes of the Secondary trial analysis, we have chosen to present the base case for all secondary repair women receiving a randomised treatment. This approach differs from that adopted for the base-case analysis of the economic analysis for women receiving a primary prolapse repair (see *Chapter 5*). The rationale for taking this alternative approach for the economic analysis of the Secondary trial data is that because of the small sample size available for the Secondary trial, the approach generates the greatest power for analysis. The approach outlined here is similar to that undertaken for the statistical analysis of the clinical outcomes data. A sensitivity analysis will explore the use of a more purist approach to analysis, including data from the three-way comparison only (i.e. RCT2A).

As with the primary repair trial analysis in *Chapter 5*, the chapter begins with a presentation of the EQ-5D-3L and QALY results, followed by costs and cost-effectiveness, measured as incremental cost per QALY gained. The analysis perspective remains that of NHS decision-makers for the base case; however, a supplementary analysis is presented, which outlines the results of the economic analysis, incorporating a wider economic perspective (including the cost of participant and companion time and travel, participant-purchased health care and wider personal and economic costs as a result of time off work because of prolapse symptoms and problems). The chapter concludes with a range of deterministic sensitivity analyses to explore uncertainty in the results presented. Where appropriate, aggregate data from the secondary repair trial will be adapted and combined with data from the Secondary CC (CC2) to populate the secondary repair arms of the economic decision-analytic model in *Chapter 9*.

Generic quality-of-life outcomes (EuroQol-5 Dimensions, quality-adjusted life-years)

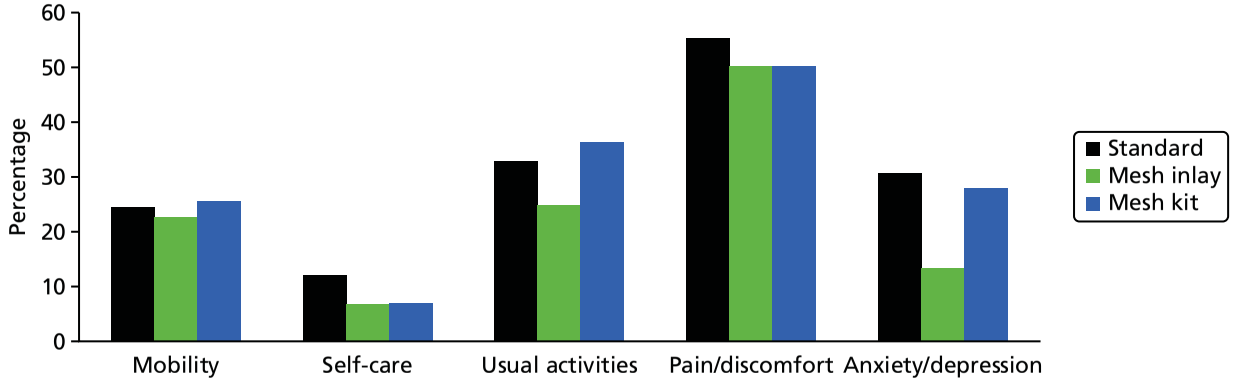
The proportion of women with any health problems reported on the EQ-5D-3L measure of generic QoL is shown in *Figures 17–19*. These figures present the data as reported by women across randomised (standard repair, mesh inlay and mesh kit) groups at 6 months, 1 year and 2 years, respectively. The descriptive data in *Figures 17–19* are based on all of the available data recorded. This contrasts with the economic evaluation data in later sections, which are based on complete cost and QALY pairs. The figures illustrate the percentage of women who were having any problems on each of the domains of QoL (i.e. women scoring a '2' or a '3'). Over half of all of the women responding to the EQ-5D-3L questionnaire report having some pain or discomfort at baseline and 1 year after surgery. There are some indications that the proportion experiencing pain and discomfort may fall after 2 years. However, because of the small sample size in the Secondary trial, it is difficult to draw any clear conclusions regarding potential differences across treatment groups and time points. Across the randomised arms, the fewest problems were experienced in self-care, with only a small proportion of women reporting any problems. A visual inspection of the graphical data appears to show some differences in the percentage of women experiencing problems; however, this variation is not consistent across time points, and there does not appear to be any systematic differences evident. Instead, the variation evident on the graph is most likely to be due to the relatively small sample size for the Secondary trial.

Figures 17–19 indicate the individual aspects of QoL that impact on overall utility for these women. *Table 68* provides the utility weights generated using time trade-off tariffs, which use population preferences to value health outcomes on a scale for which '1' represents full health and '0' represents death. These utility values



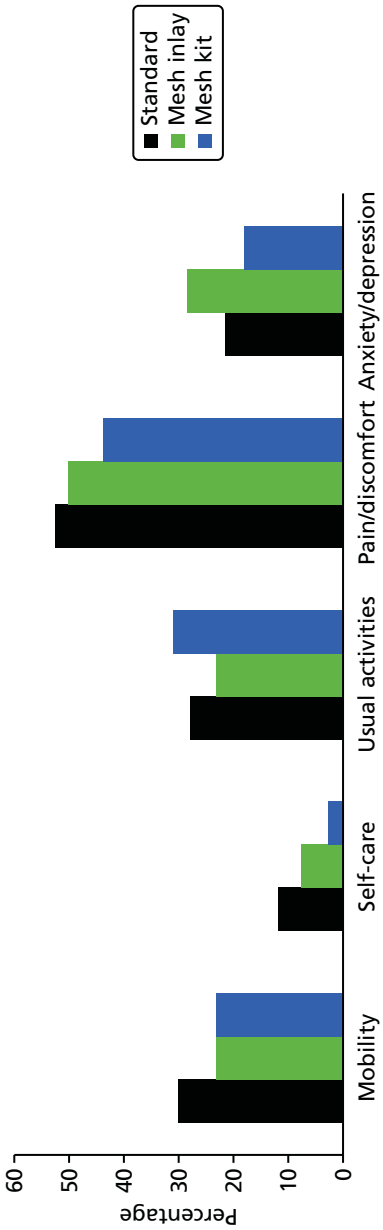
Standard *n*/*N* (%)	13/49 (26.53)	3/49 (6.12)	12/49 (24.49)	25/49 (51.02)	10/48 (20.83)
Mesh inlay *n*/*N* (%)	10/47 (21.28)	2/46 (4.35)	12/46 (26.08)	24/46 (52.17)	7/46 (15.21)
Mesh kit *n*/*N* (%)	8/42 (19.05)	3/42 (7.14)	13/42 (30.95)	24/42 (57.14)	8/42 (19.05)

FIGURE 17 Proportion of women experiencing any problems on each EQ-5D domain at 6 months. Analysis based on all of the available EQ-5D data points.



Standard *n*/*N* (%)	12/49 (24.49)	6/49 (12.24)	16/49 (32.65)	27/49 (55.1)	15/49 (30.61)
Mesh inlay *n*/*N* (%)	10/44 (22.73)	3/43 (6.98)	11/44 (25)	22/44 (50)	6/44 (13.64)
Mesh kit *n*/*N* (%)	11/43 (25.58)	3/42 (7.14)	16/44 (36.36)	22/44 (50)	12/43 (27.91)

FIGURE 18 Proportion of women experiencing any problems on each EQ-5D domain at 1 year. Analysis based on all of the available EQ-5D data points.



	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Standard *n/N* (%)	13/43 (30.23)	5/43 (11.63)	12/43 (27.91)	22/42 (52.38)	9/42 (21.43)
Mesh inlay *n/N* (%)	9/39 (23.08)	3/39 (7.69)	9/39 (23.08)	19/38 (50)	11/39 (28.21)
Mesh kit *n/N* (%)	9/39 (23.08)	1/38 (2.63)	12/39 (30.77)	17/39 (43.59)	7/39 (17.95)

FIGURE 19 Proportion of women experiencing any problems on each EQ-5D domain at 2 years. Analysis based on all of the available EQ-5D data points.

TABLE 68 EuroQol-5 Dimentions (3-level version) at each time point: Secondary trial

Treatment group	Standard pair: mean (SD); *n*	Mesh Iay: mean (SD); *n*	Mesh kit: mean (SD); *n*
EQ-5D: baseline	0.641 (0.296); 52	0.749 (0.161); 50	0.692 (0.238); 42
EQ-5D: 6 months	0.769 (0.306); 48	0.826 (0.209); 46	0.771 (0.263); 42
EQ-5D: 12 months	0.743 (0.304); 50	0.830 (0.218); 43	0.827 (0.194); 41
QALYs gained[a] (baseline to 1 year)	*0.727 (0.268); 45*	*0.816 (0.148); 42*	*0.764 (0.191); 38*
EQ-5D: 24 months	0.764 (0.294); 42	0.818 (0.194); 38	0.867 (0.142); 38
QALYs gained[a] (baseline to 2 years)	*1.476 (0.501); 38*	*1.606 (0.332); 35*	*1.614 (0.306); 34*

a QALYs gained are based on an area-under-the-curve analysis, whereas EQ-5D utilities are point estimates at the follow-up time points. QALYs in the second year are discounted at a rate of 3.5% per annum.

are used for QALY calculations. Note that in *Table 68*, data are presented for summary statistics for all of the randomised women to the Secondary trial (i.e. all women randomised to RCT2).

On initial visual inspection of the data, it would appear as if QALYs for the mesh inlay and mesh kit groups are substantially higher than in the standard repair group (discounted 2-year QALY = 1.476). However, these results should be considered in the light of substantial variation across secondary repair women who also reported better health outcomes on the EQ-5D-3L at baseline. It is important, therefore, to adjust QALY estimates for these baseline imbalances across groups. *Table 69* presents these incremental QALYs gained as two effect sizes: the first for mesh inlay compared with standard repair and the second for mesh kit compared with standard repair. The estimates of QALYs gained are based on non-parametric bootstrapped linear regression (OLS) models, with adjustment for baseline covariates, including baseline EQ-5D-3L score, centre, age, BMI, concomitant continence procedure at baseline and compartment of prolapse. Additionally, the analysis model includes a fixed effect for randomised stratum. Analyses were conducted using heteroscedastic robust SEs.

There were no differences in QALYs between treatment groups at 1 year or 2 years. As with the Primary trial analysis, baseline EQ-5D-3L utility score was a significant predictor of overall QALYs, thus emphasising the importance of controlling for baseline utility when estimating QALY gains or losses between treatment groups. None of the other variables included in the estimation models was found to have a significant effect on QALYs gained. Overall, there is no evidence of any difference in generic QoL or QALYs between

TABLE 69 Incremental QALYs (all Secondary trial women)

	Outcomes					
	1 year			2 year[a]		
QALYs	Mean (SD); *n*	Raw MD (vs. standard)	Adj. MD (vs. standard) (95% CI)[b]	Mean (SD); *n*	Raw MD (vs. standard)	Adjusted MD (vs. standard) (95% CI)[b]
Standard repair	0.727 (0.268); 45			1.476 (0.501); 38		
Mesh inlay	0.816 (0.148); 42	0.089	0.011 (–0.061 to 0.084)	1.606 (0.332); 35	0.13	0.018 (–0.149 to 0.185)
Mesh kit	0.764 (0.191); 38	0.037	–0.011 (–0.086 to 0.064)	1.614 (0.306); 34	0.138	0.096 (–0.081 to 0.274)

a QALYs in second year discounted at 3.5% per annum.
b Regression analysis based on non-parametric bootstrapped OLS regression, with adjustment for age, BMI, whether the centre was a main lead site (Aberdeen, Manchester and Plymouth), concomitant continence procedure, anterior prolapse or baseline utility. Heteroscedastic robust SEs are used.

randomised groups over the follow-up period. The lack of any significant effect is likely to be due, in part, to the small sample size recruited to RCT2. Based on current evidence, there is insufficient information to definitively determine a favourable treatment approach for secondary prolapse repair in terms of QALYs gained and further research is required to determine the repair strategy that generates greatest QALY improvement for women who were having a secondary surgical prolapse repair. Despite uncertainty regarding the most beneficial strategy in terms of QALYs gained, it is important to consider this uncertainty alongside cost implications of different surgeries within a cost-effectiveness analysis framework.

NHS resource use and costs

Costs to health services

This section outlines the results of our analysis for costs to the health services of alternative strategies for secondary prolapse repair surgery. Costs include intervention procedure costs, inpatient and follow-up secondary care costs, and costs of primary care services relating to the prolapse surgery. This may include, for example, treatment of complications, treatment failure or increased contact with health-care professionals for prolapse-related issues. The descriptive statistics and the regression analyses are based on complete case cost data for all women who were having a secondary prolapse repair (RCT2). The total NHS costs are calculated by multiplying resource use by the appropriate unit cost estimates outlined in *Table 2* (see *Chapter 2*).

Intervention costs

Table 70 reports the total intervention costs for each of the secondary surgical prolapse repairs considered.

All surgical procedures had similar costs associated with staff requirements, time in theatre and overheads to complete the respective procedures. Regarding the cost of materials, mesh kits were the most costly, followed by mesh inlays and standard repair. Summing these components together, there was no statistically significant difference in total intervention cost between mesh inlay and standard repair. However, this is probably because of the small sample size. Owing to the substantial additional cost of mesh kit materials, the total intervention cost for mesh kits was statistically significantly higher than a standard repair. It should be noted that the cost of materials for secondary mesh interventions were highly variable across centres and suppliers, as is evident in the large SDs reported. These analyses make no statements about the effectiveness or cost-effectiveness of one mesh inlay material relative to another, or one type of mesh kit relative to another.

Health services resource-use costs over trial follow-up

The additional costs of mesh procedures (in particular mesh kits) are combined with costs to the health services over the trial follow-up period for each treatment group and are presented in *Table 71*. These include all secondary care (readmissions, reoperations, visits to ward, outpatient consultations) and primary care (e.g. GP, nurse, physiotherapist) contacts with health professionals. We have taken the following approach to the presentation of cost data. Each category of cost is presented for full cases within that category (e.g. hospital resource use, primary care costs). These are then summed, along with the intervention cost, for complete cases across all of the categories, and presented as the total cost to the health services at 2 years. Data presented in *Table 71* and for the statistical analyses are based on all women who were randomised to receive a secondary repair surgery (i.e. all women randomised to RCT2). Owing to the small sample size, non-parametric bootstrapping is used to create CIs around MDs in costs. Regression models include a fixed effect for randomised stratum and heteroscedastic robust SEs are used for all models. The costs presented are presented in accordance with the assumptions outlined in *Chapter 2* regarding handling of missing data.

At 1 year post operation, based on the data available from the Secondary trial, mesh kits are significantly more costly than the standard repair and are the most costly of the three treatment options. There were no significant differences between mesh inlays and standard repair in 1-year total costs to the health services. The cost results are primarily driven by the additional intervention cost of mesh kit repairs as outlined in the preceding section.

TABLE 70 Intervention costs: Secondary trial

	Standard repair			Mesh inlay			Mesh kit			Incremental analysis[a]	
Intervention costs	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mesh inlay vs. standard (£): MD (95% CI)	Mesh kit vs. standard (£): MD (95% CI)
Mesh cost	17	89	55	128	175	51	609	400	45		
Staff time in theatre	818	370	55	859	281	52	856	329	46		
Cost of drugs in theatre	25	7	55	24	8	52	25	8	46		
Cost of catheterisation	6	2	55	6	2	52	6	1	46		
Cost of vaginal packing	4	2	55	4	2	52	4	2	46		
Theatre overheads	414	169	55	435	133	52	448	164	46		
Subtotal: theatre costs	*1282*	*551*	*55*	*1457*	*498*	*51*	*1949*	*632*	*45*		
Costs from theatre: discharge	1508	1139	55	1642	1214	51	1573	1069	45		
Total intervention costs	*2790*	*1295*	*55*	*3099*	*1358*	*51*	*3522*	*1100*	*45*	*398 (–197 to 993)*	*914 (349 to 1478)*

a Regression analysis based on non-parametric bootstrapped OLS regression, with adjustment for age, BMI, whether the centre was a main lead site (Aberdeen, Manchester and Plymouth), concomitant continence procedure, anterior prolapse or baseline utility. Heteroscedastic robust SEs are used.

TABLE 71 Health-care resource use and costs: NHS perspective – Secondary trial

NHS resource use and costs	Resource use: *n*/*N* (%)			Costs[a]				
							Incremental analysis of costs (£)[b]	
	Standard repair	Mesh inlay	Mesh kit	Standard repair: mean (SD); *N*	Mesh inlay: mean (SD); *N*	Mesh kit: mean (SD); *N*	Mesh inlay vs. standard	Mesh kit vs. standard
Total intervention costs	–	–	–	2790 (1295); 55	3099 (1358); 51	3522 (1100); 45	398 (–197 to 993)	914 (349 to 1478)
1-year data								
Hospital resource use (0–6 months)								
New prolapse procedure	0/50 (0.0)	0/47 (0.0)	1/43 (2.3)					
New incontinence procedure	0/50 (0.0)	0/47 (0.0)	0/43 (0.0)					
Other related readmissions	2/50 (4.0)	5/47 (10.6)	1/43 (2.3)					
Further prolapse-related surgery within 6 months	*2/50 (4.0)*	*5/47 (10.6)*	*2/43 (4.7)*	*40 (203); 50*	*120 (355); 47*	*54 (355); 43*		
Outpatient visits: with any visit[b]	4/50 (8.0)	3/47 (6.4)	4/43 (9.3)	11 (36); 50	8 (33); 47	12 (39); 43		
Subtotal (hospital use 0–6 months)	–	–	–	*51 (204); 50*	*128 (354); 47*	*67 (356); 43*	*98 (–40 to 237)*	*86 (–53 to 224)*
Hospital resource use (6–12 months)								
New prolapse procedure:	3/49 (6.1)	1/44 (2.3)	0/44 (0.0)	143 (565); 49	53 (351); 44	0 (0); 44		
New incontinence procedure	0/49 (0.0)	1/44 (2.3)	2/44 (4.5)	0 (0); 49	31 (207); 44	62 (289); 44		
Other related readmissions	0/49 (0.0)	2/44 (4.5)	2/44 (4.5)	0 (0); 49	55 (255); 44	55 (255); 44		
Outpatient visits[b]	0.59 (1.04)	0.66 (1.14)	0.64 (0.97)	67 (103); 49	72 (113); 44	67 (98); 44		
Subtotal (hospital use 6–12 months)	–	–	–	*210 (612); 49*	*211 (481); 44*	*184 (409); 44*	*–38 (–290 to 213)*	*11 (–243 to 264)*
Other consultations (0–12 months)								
Physiotherapy[b]	0.08 (0.4)	1.11 (3.20)	0.11 (0.54)	2 (10); 49	27 (77); 44	3 (13); 44		
GP nurse[b]	0.04 (0.29)	0.20 (0.70)	0 (0)	1 (4); 49	3 (10); 44	0 (0); 44		
GP doctor[b]	0.55 (1.24)	0.77 (1.36)	0.98 (3.75)	25 (57); 49	36 (63); 44	45 (173); 44		
Other[b]	0.11 (0.48)	0.05 (0.30)	0 (0)	6 (28); 49	8 (56); 44	0 (0); 44		

continued

TABLE 71 Health-care resource use and costs: NHS perspective – Secondary trial (*continued*)

	Resource use: *n*/*N* (%)			Costs[a]				
							Incremental analysis of costs (£)[b]	
NHS resource use and costs	Standard repair	Mesh inlay	Mesh kit	Standard repair: mean (SD); *N*	Mesh inlay: mean (SD); *N*	Mesh kit: mean (SD); *N*	Mesh inlay vs. standard	Mesh kit vs. standard
Subtotal (other consultations 0–12 months)	–	–	–	*34 (65); 49*	*73 (111); 44*	*48 (175); 44*	*41 (–3 to 84)*	*44 (–49 to 137)*
Other treatments (0–12 months)								
Shelf pessary	0/49 (0.0)	0/44 (0.0)	0/44 (0.0)	0 (0); 49	0 (0); 44	0 (0); 44		
Ring pessary	0/49 (0.0)	0/44 (0.0)	0/44 (0.0)	0 (0); 49	0 (0); 44	0 (0); 44		
Incontinence drugs	6/49 (12.2)	9/44 (20.5)	6/44 (13.6)	4 (10); 49	6 (12); 44	6 (11); 44		
Oestrogen	13/49 (26.5)	15/44 (34.1)	12/44 (27.3)	5 (8); 49	6 (9); 44	5 (9); 44		
Intermittent catheters	2/49 (4.1)	0/44 (0.0)	1/44 (2.3)	74 (363); 49	0 (0); 44	41 (274); 44		
Permanent catheter	1/49 (2.0)	0/44 (0.0)	0/44 (0.0)	8 (56); 49	0 (0); 44	0 (0); 44		
Absorbent pads	18/49 (36.7)	16/44 (36.4)	13/44 (29.5)	211 (296); 49	226 (327); 44	277 (465); 44		
Other drug treatments	1/49 (2.0)	3/44 (6.8)	0/44 (0.0)	1 (9); 49	0 (1); 44	0 (0); 44		
Subtotal (other treatments 0–12 months)	–	–	–	*304 (512); 49*	*238 (332); 44*	*329 (523); 44*	*–71 (–288 to 147)*	*–18 (–256 to 221)*
Total 1-year follow-up costs	**–**	**–**	**–**	**607 (913); 47**	**657 (773); 44**	**580 (684); 43**	**9 (–387 to 405)**	**15 (–362 to 392)**
Total health services costs (1 year)	**–**	**–**	**–**	**3423 (1596); 47**	**3675 (1787); 44**	**4104 (1376); 43**	**421 (–397 to 1239)**	**996 (296 to 1697)**
2-year data *Hospital resource use (12–24 months)*								
New prolapse procedure	4/43 (9.3)	3/38 (7.9)	1/39 (2.6)	210 (662); 43	178 (615); 38	58 (361); 39		
New incontinence procedure	0/43 (0.0)	1/38 (2.6)	2/39 (5.1)	0 (0); 43	35 (215); 38	68 (296); 39		
Other related readmissions	0/43 (0.0)	2/38 (5.3)	0/39 (0.0)	0 (0); 43	51 (225); 38	0 (0); 39		
Outpatient visits[b]	0.21 (0.47)	0.26 (0.55)	0.15 (0.49)	20 (44); 43	25 (54); 39	16 (51); 39		

NHS resource use and costs	Resource use: *n*/*N* (%)			Costs[a]				
							Incremental analysis of costs (£)[b]	
	Standard repair	Mesh inlay	Mesh kit	Standard repair: mean (SD); *N*	Mesh inlay: mean (SD); *N*	Mesh kit: mean (SD); *N*	Mesh inlay vs. standard	Mesh kit vs. standard
Subtotal (hospital resource use 12–24 months)	–	–	–	*229 (663); 43*	*288 (683); 38*	*142 (456); 39*	*–111 (–473 to 251)*	*–161 (–470 to 148)*
Other consultations (12–24 months)								
Physiotherapy[a]	0.05 (0.21)	0.64 (3.25)	0.18 (0.85)	1 (5); 43	15 (75); 39	4 (20); 39		
GP nurse[a]	0.19 (0.63)	0(0)	0(0)	2 (8); 43	0 (0); 39	0 (0); 39		
GP doctor[a]	0.19 (0.70)	0.31 (1.06)	0.77 (4.33)	8 (31); 43	14 (47); 39	34 (192); 39		
Other[a]	0.05 (0.31)	0.08 (0.35)	0(0)	1 (7); 42	1 (3); 39	0 (0); 39		
Subtotal other consultations (12–24 months)	–	–	–	*13 (36); 42*	*29 (99); 39*	*38 (211); 39*	*7 (–28 to 42)*	*–3 (–22 to 16)*
Other treatments (12–24 months)								
Shelf pessary	3/43 (7.0)	1/39 (2.6)	0/39 (0.0)	4 (16); 43	2 (10); 39	0 (0); 39		
Ring pessary	2/43 (4.7)	1/39 (2.6)	1/39 (2.6)	2 (8); 43	1 (6); 39	1 (6); 39		
Incontinence drugs	6/43 (14.0)	7/38 (18.4)	6/39 (15.4)	5 (9); 43	7 (12); 38	5 (12); 39		
Oestrogen	7/46 (15.2)	11/40 (27.5)	9/39 (23.1)	7 (10); 46	10 (11); 40	8 (11); 39		
Intermittent catheters	1/43 (2.3)	0/38 (0.0)	1/39 (2.6)	41 (268); 43	0 (0); 38	45 (281); 39		
Permanent catheter	0/43 (0.0)	0/38 (0.0)	0/39 (0.0)	0 (0); 43	0 (0); 38	0 (0); 39		
Absorbent pads	12/43 (27.9)	8/38 (21.1)	10/39 (25.6)	209 (366); 43	141 (301); 38	260 (630); 39		
Other drug treatments	2/43 (4.7)	2/38 (5.3)	1/39 (2.6)	1 (6); 43	10 (56); 38	0 (1); 39		
Subtotal, other treatments (12–24 months)	–	–	–	*268 (433); 43*	*167 (307); 38*	*319 (677); 39*	*2 (–171 to 175)*	*130 (–111 to 371)*
Total 2-year follow-up costs (12–24 months)	**–**	**–**	**–**	**521 (738); 42**	**485 (797); 38**	**499 (895); 39**	**–101 (–512 to 310)**	**–35 (–441 to 371)**
Total health services costs (2 years)	**–**	**–**	**–**	**3815 (2019); 41**	**4051 (2098); 37**	**4495 (1739); 39**	**238 (–929 to 1405)**	**873 (–27 to 1774)**

a Costs in second year discounted at a rate of 3.5% per annum.
b Incremental analyses are based on data from RCT2. Analysis models are adjusted for minimisation covariates (age group, type of prolapse, concomitant incontinence procedure and concomitant upper compartment prolapse surgery), as well as surgeon and baseline EQ-5D-3L score.

At 2-year follow-up, based on the data available from RCT2, there is some (weak; $p < 0.1$) evidence to suggest that women who were randomised to the mesh kit group incurred greater costs than standard repair. On average, mesh kits were £873 more costly than standard repair (95% CI –£27 to £1774). These additional costs to the health services was driven almost entirely by differences in the price of the original mesh product used for the surgical procedure. This evidence, although classified as weak, is based on a very small sample size, and is indicative of the substantial extra costs associated with the mesh kit intervention. There was not enough evidence to make any statements on the differences in treatment costs for the comparison of mesh inlay with standard repair. Incremental costs are £238 (95% CI –£929 to £1405). It should be noted that this estimate of incremental health services costs is surrounded by substantial uncertainty, large SDs and wide CIs.

Base-case cost-effectiveness results (NHS perspective)

Although there are no clear differences in costs evident as a result of the uncertainty surrounding estimates of incremental costs, it is important to consider the joint uncertainty across costs and outcomes within a cost-effectiveness analysis framework. The base-case economic (cost–utility) analysis is presented according to the regression models outlined for costs and QALYs in the methods section (see *Chapter 2*) and the presentation of results follows a similar approach to that of the Primary trial cost-effectiveness analysis. The base-case economic analysis is presented for complete case data of cost and QALY pairs, ensuring that the joint distribution of costs and effects is not broken. As with the data presented in previous tables, all analyses are for all women who were randomised to the Secondary trial comparison (RCT2). Owing to the small sample size, alternative combinations of costs and QALYs will be explored (e.g. considering complete case cost and complete case QALY data separately).

Cost-effectiveness results

One-year cost-effectiveness results

Table 72 presents the main results of the economic analysis from a NHS perspective over a 1-year time horizon. An initial interpretation of the results suggests that, based on ICERs presented, over a 1-year time horizon, neither mesh inlays nor mesh kits would offer a cost-effective use of NHS resources, based on commonly accepted threshold values of WTP for a QALY gained, set at between £20,000 and £30,000 per QALY. Data are based on complete case analysis of cost and QALY pairs. Owing to the small sample size, the point estimates of the ICERs are based on highly uncertain data, and estimates of incremental costs and QALYs that are surrounded by very wide CIs. Therefore, point estimates of the ICER are not particularly meaningful for the Secondary trial analysis and should be interpreted in light of the uncertainty surrounding them. Based on the data presented in the tables, there is insufficient evidence to draw any clear cost-effectiveness conclusions regarding the most cost-effective secondary repair strategy. The most appropriate interpretation of the cost-effectiveness data can be made using the simulations from the bootstrapped estimates of incremental costs and QALYs, with 1000 repetitions. *Figure 20* illustrates the scatterplot of incremental costs and incremental QALYs for the 1-year analysis of the Secondary trial data for mesh inlay compared with standard repair, and also for mesh kit versus standard repair, although *Figure 21* shows the CEACs, illustrating the probability of each strategy being cost-effective at alternative threshold values of WTP for a QALY gained. As can be seen from these figures, there is great uncertainty surrounding the optimal strategy in terms of cost-effectiveness. Using data presented in the CEACs, the probability of the interventions being cost-effective over a 1-year time horizon are as follows: standard repair (55%), mesh inlay (39%) and mesh kits (6%), demonstrating that there is no clearly cost-effective strategy, based on the current data. The only reasonable conclusion to draw from these data is that mesh kits do not appear to be cost-effective over 1 year. This is because of the substantial additional cost of the kits themselves.

TABLE 72 Base-case cost-effectiveness results: Secondary trial – complete case data (1 year)

Treatment	Costs: mean (SD)[a]	Incremental costs (vs. standard)	QALYs: mean (SD)[a]	Incremental QALYs (vs. standard)	Incremental cost (£) per QALY gained (vs. standard)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[b]				
						£0	£10k	£20k	£30k	£50k
Standard repair ($n = 44$)	3454 (1639)	–	0.728 (0.272)	–	–	0.84	0.74	0.64	0.55	0.48
Mesh inlay ($n = 42$)	3734 (1808)	471 (–404 to 1346)	0.816 (0.148)	0.007 (–0.060 to 0.074)	*67,286*	0.16	0.24	0.33	0.39	0.44
Mesh kits ($n = 38$)	4165 (1386)	933 (200 to 1665)	0.764 (0.191)	–0.017 (–0.086 to 0.052)	*Dominated*	0.00	0.02	0.04	0.06	0.08

a Note that the estimates of costs, QALYs and incremental costs and QALY s will differ from the tables reported above, as these are based on complete case data for cost and QALY pairs.
b Owing to rounding, values in probability may add to 0.99 or 1.01.

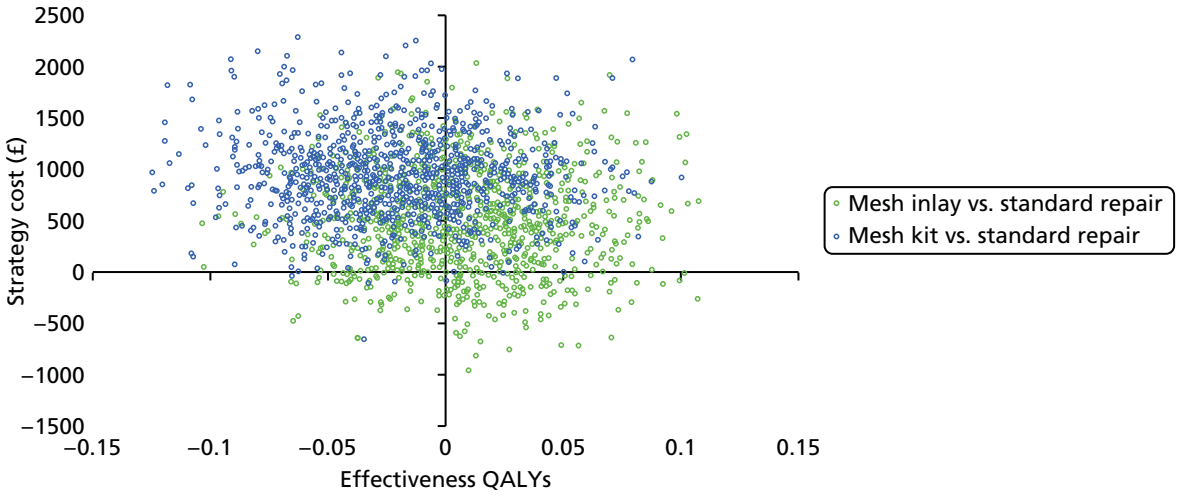


FIGURE 20 Scatterplot of incremental costs and QALYs for mesh treatments compared with standard repair: secondary prolapse repair (1-year follow-up data).

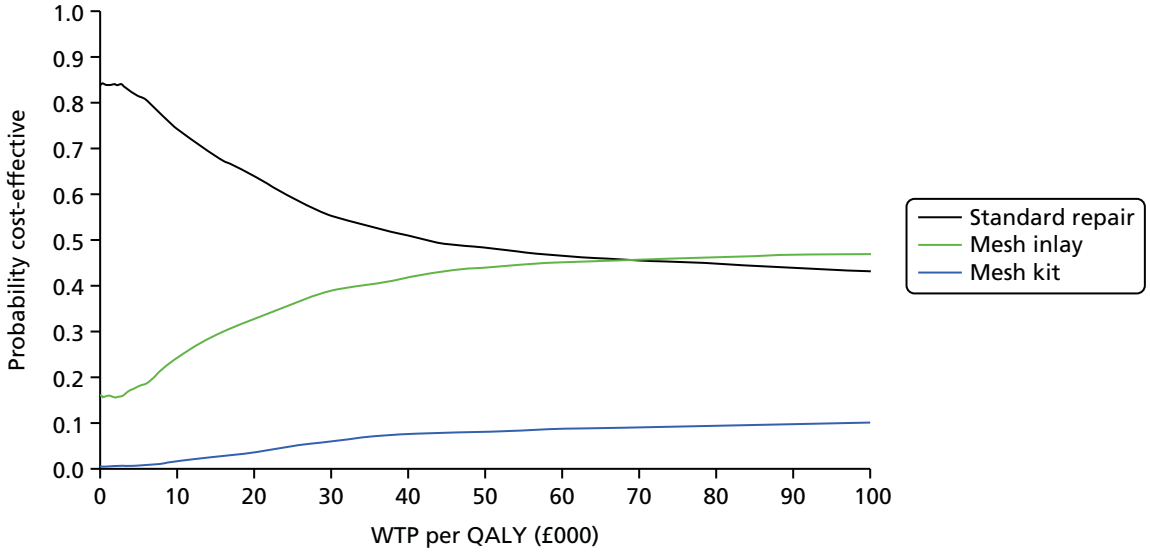


FIGURE 21 Cost-effectiveness acceptability curves: secondary prolapse repair (1-year follow-up data).

Two-year cost-effectiveness results

The results of the analysis over a 2-year time horizon, with costs and QALYs in the second year discounted at a rate of 3.5% per annum, are presented in *Table 73* and *Figures 22* and *23* for the base-case results, scatterplots of incremental cost-effectiveness and CEACs, respectively. Considering the same £30,000 threshold value of WTP for a QALY gained, the probability of cost-effectiveness for each treatment strategy is as follows: standard repair (32%), mesh inlay (19%) and mesh kit (49%). Based on the current data, at 2 years' follow-up the mesh kits are the most likely to be cost-effective, followed by standard repair and mesh inlay. There is insufficient evidence, however, to clearly recommend any one treatment strategy for secondary prolapse repair, based on the data available, as none of the treatment strategies is definitively cost-effective. The figures illustrate that the estimates of incremental costs and QALYs are surrounded by considerable uncertainty as a result of the small sample size for the Secondary trial. Further research, based on larger samples, is required to definitively determine the most cost-effective strategy for women who were having a secondary prolapse repair.

TABLE 73 Base-case cost-effectiveness results: Secondary trial – complete case data (2 years)

Treatment	Costs: mean (SD)[a]	Incremental costs (vs. standard)	QALYs: mean (SD)[a]	Incremental QALYs (vs. standard)	Incremental cost (£) per QALY gained (vs. standard)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[b]				
						£0	£10,000	£20,000	£30,000	£50,000
Standard repair ($n = 36$)	3883 (2127)		1.486 (0.493)			0.57	0.45	0.36	0.32	0.29
Mesh inlay ($n = 34$)	4133 (2153)	236 (–1091 to 1564)	1.600 (0.335)	–0.023 (–0.163 to 0.118)	*Dominated*	0.38	0.24	0.21	0.19	0.18
Mesh kit ($n = 34$)	4528 (1721)	642 (–309 to 1592)	1.614 (0.306)	0.050 (–0.085 to 0.185)	*12,840*	0.05	0.31	0.44	0.49	0.53

a Note that the estimates of costs, QALYs and incremental costs and QALY s will differ from the tables reported above, as these are based on complete case data for cost and QALY pairs.
b Owing to rounding, values in probability may add to 0.99 or 1.01.

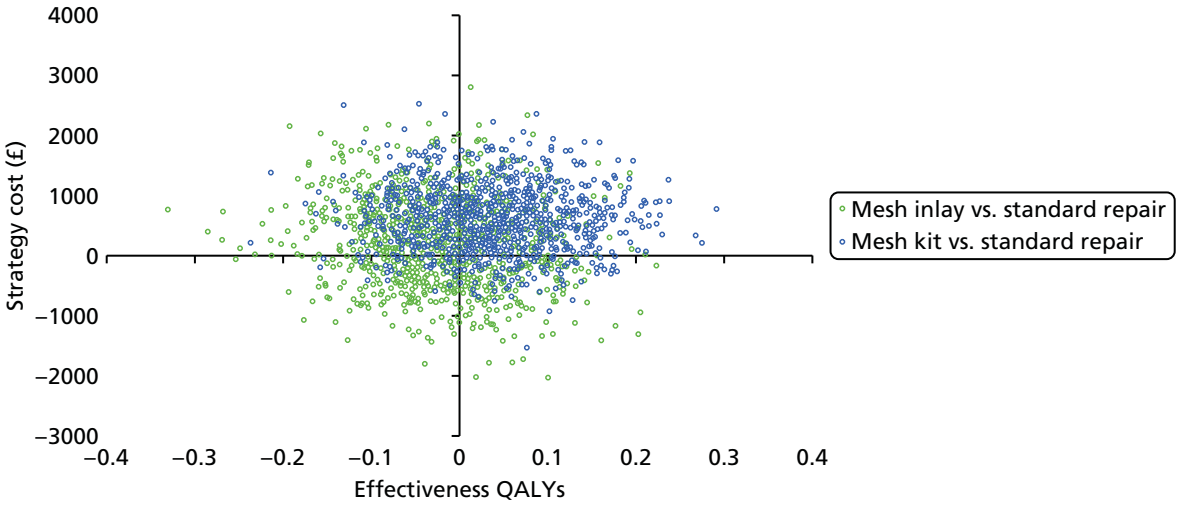


FIGURE 22 Scatterplot of incremental costs and QALYs for mesh treatments compared with standard repair: secondary prolapse repair (2-year follow-up data).

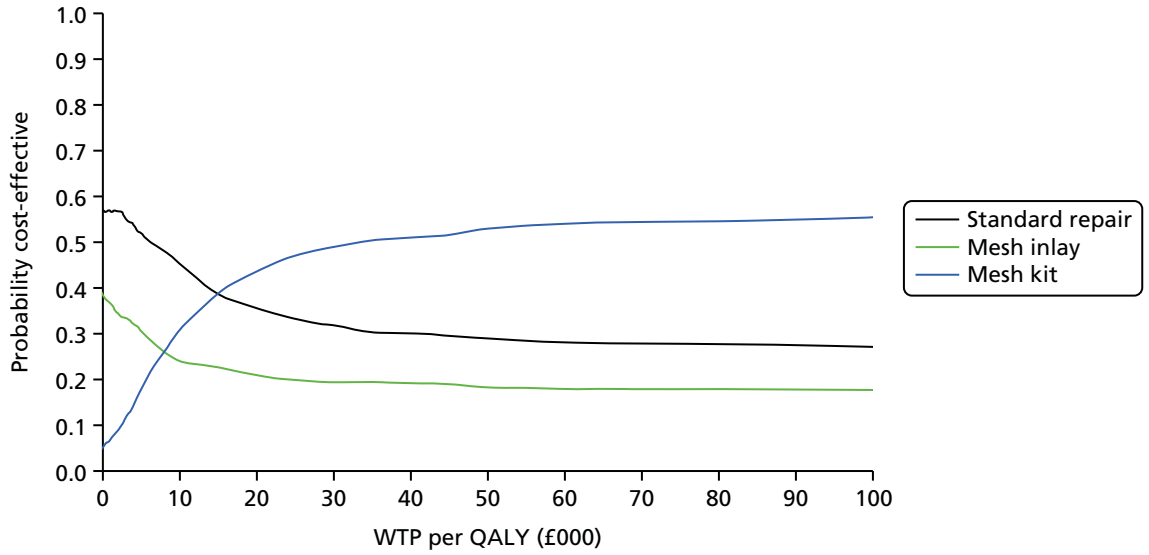


FIGURE 23 Cost-effectiveness acceptability curves: secondary prolapse repair (2-year follow-up data).

As with the Primary trial analysis, the true clinical effectiveness and cost-effectiveness of mesh materials for secondary prolapse repair cannot be determined by such a short time horizon, which may be insufficient to capture longer-term risk of recurrence and any associated complications. Longer-term data are thus required on costs and QALYs to accurately determine cost-effectiveness. Currently, the data available for secondary repairs are too sparse to populate an accurate economic modelled projection of longer-term outcomes, with too few data to develop time to effect analysis for probability of failures and serious complications. We therefore await the completion of longer-term follow-up of PROSPECT women to determine a more accurate estimate of cost-effectiveness for secondary prolapse repair.

Costs directly incurred by participants and indirect costs

A further analysis was conducted incorporating both participant and indirect costs into the analysis.

Table 74 reports mean costs (from a wider economic perspective) of attending primary care, outpatient appointments and inpatient admissions, respectively. Inpatient admissions also includes participant-incurred costs for attending their PROSPECT surgery. As well as admissions for surgery (main PROSPECT surgery and

TABLE 74 Participant, companion and indirect costs for women who were having a secondary prolapse repair

	Standard repair			Mesh inlay			Mesh kit			Incremental analysis	
Costs	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mean (£)	SD (£)	*n*	Mesh inlay vs. standard: MD (95% CI)	Mesh kit vs. standard: MD (95% CI)
Time off work due to prolapse problems	707	2485	49	1017	3424	45	805	3244	44	424 (–1115 to 1965)	39 (–1486 to 1564)
Participant and companion time and travel costs (primary care appointments)	10	20	42	23	40	34	20	88	39	9 (–7 to 26)	–4 (–15 to 8)
Participant and companion time and travel costs (outpatient appointments)	39	87	39	19	24	30	44	62	32	–21 (–52 to 10)	27 (–1 to 54)
Participant and companion time and travel costs (inpatient appointments)	283	210	55	262	129	51	272	152	45	–19 (–99 to 61)	–20 (–102 to 63)
Self-purchased health care and medication	4	22	48	0	2	45	6	37	43	–4 (–12 to 4)	–1 (–7 to 4)
Total indirect and participant costs	**952**	**2428**	**55**	**1186**	**3235**	**51**	**1114**	**3224**	**45**	**228 (–1120 to 1577)**	**77 (–1356 to 1510)**
Total NHS cost (2 years)	**3815**	**2019**	**41**	**4051**	**2098**	**37**	**4495**	**1739**	**39**	**238 (–929 to 1405)**	**873 (–27 to 1774)**
Overall total NHS, participant and indirect costs	**4905**	**4079**	**41**	**5572**	**4698**	**37**	**5222**	**2485**	**39**	**935 (–1347 to 3218)**	**499 (–1482 to 2481)**

Data are based on all Secondary trial women (randomised to RCT2); year 2 costs are discounted at a rate of 3.5% per annum.

any follow-up admissions) and outpatient consultations, PROSPECT women who were having a secondary repair also experienced a large number of primary care consultations, either with GPs, practice nurses, specialist nurses or physiotherapists. As a result, the economic cost of time spent travelling to, and attending, appointments for participants and their companions (if they reported being accompanied on a visit) was substantial. However, there was no evidence of any differences across randomised groups, and it is important to note large SDs, which indicate great uncertainty in participant time and travel costs across the groups. However, one should also consider that the estimates are highly uncertain and based on very small sample sizes.

Furthermore, a small proportion of women incurred direct private health-care costs or self-purchased medication. However, the majority did not and there were no differences across groups.

Mean indirect costs of sick leave taken as a result of prolapse symptoms were £707, £1017 and £805 per woman for standard repair, mesh inlay and mesh kits, respectively, over the 2-year trial period. The large values reflect the fact that prolapse symptoms have a substantial impact on everyday life for women in terms of financial consequences. However, there were no differences across the randomised groups in terms of time taken as sick leave in relation to prolapse problems and symptoms. The wider economic impact is likely to be greater still if one were to consider the lost productivity of days spent at work, where bothersome symptoms interfered with women's normal work activities but may not necessarily have required sick leave. Therefore, the estimates of true economic cost are likely to be underestimated.

Combining all of the costs of sick leave, opportunity costs of time for participants and companions to attend appointments, travel costs to attend appointments and total costs to the NHS, we can estimate a wider overall economic cost to society. This is, of course, limited to the costs considered and the true economic costs may be much higher. Nonetheless, the analysis gives an overall impression of the most immediate wider economic costs associated with prolapse surgery and the alternative treatment options considered in the PROSPECT trial. Total economic costs were estimated as £4905, £5572 and £5222 for standard repair, mesh inlay and mesh kit, respectively. There were no differences between groups either for the total economic costs or for any individual component of travel, time or productivity costs.

Incorporating indirect costs and economic productivity losses of time off work into the analysis of costs significantly increases the cost burden to society, showing that the costs of prolapse treatment go far beyond the health service implications. Incorporating these estimates into the overall cost-effectiveness, from a wider and more societal perspective of analysis, further increases the uncertainty for an analysis that was already highly uncertain due to the small sample recruited to the Secondary trial. The results of the analysis incorporating wider economic costs is presented in *Table 75*, with large SDs surrounding estimates of overall economic costs.

To further explore the impact of the wider costing approach on conclusions, and in the light of the significant uncertainty, it is best to interpret the results using the scatterplot of incremental costs and effectiveness for mesh inlay and mesh kits (compared with standard repair), as well as the CEAC calculated using the net benefit statistic derived from the results of 1000 bootstrapped replicates of mean costs and QALYs. *Figures 24* and *25* illustrate that the probabilities of standard repair, mesh inlay and mesh kit being the most cost-effective treatment strategy at a threshold value of WTP for a QALY gained of £30,000 are 33%, 11% and 56%, respectively.

The uncertainty surrounding both the NHS and participant-incurred costs, as well as uncertain QALY gains, means that there is insufficient evidence to draw conclusions on cost-effectiveness from a wider economic perspective for women who were having their second prolapse repair surgery.

TABLE 75 Base-case cost-effectiveness results (incorporating a wider economic perspective): secondary prolapse repair

Treatment	Costs (£): mean (SD)[a]	Incremental costs (£) vs. standard: MD (95% CI)	QALYs: mean (SD)[a]	Incremental QALYs (vs. standard): MD (95% CI)	Incremental cost (£) per QALY gained (vs. standard) (£per QALY)	Probability of cost-effectiveness at alternative threshold values of WTP for a QALY gain (%)[b]				
						£0	£10,000	£20,000	£30,000	£50,000
Standard repair ($n = 36$)	3883 (2127)		1.486 (0.493)			0.52	0.42	0.35	0.33	0.30
Mesh inlay ($n = 34$)	4133 (2153)	1030 (–1525 to 3586)	1.600 (0.335)	–0.023 (–0.163 to 0.118)	*Dominated*	0.14	0.10	0.11	0.11	0.12
Mesh kit ($n = 34$)	4528 (1721)	293 (–1839 to 2426)	1.614 (0.306)	0.050 (–0.085 to 0.185)	*5860*	0.34	0.48	0.54	0.56	0.58

a Results based on costs and QALYs discounted by 3.5% per annum in the second year.
b Owing to rounding, values in probability may add to 0.99 or 1.01.
Based on complete case data for wider economic costs and QALY gains pairs (therefore, each treatment '*n*' might not be the same as base-case analysis, above).

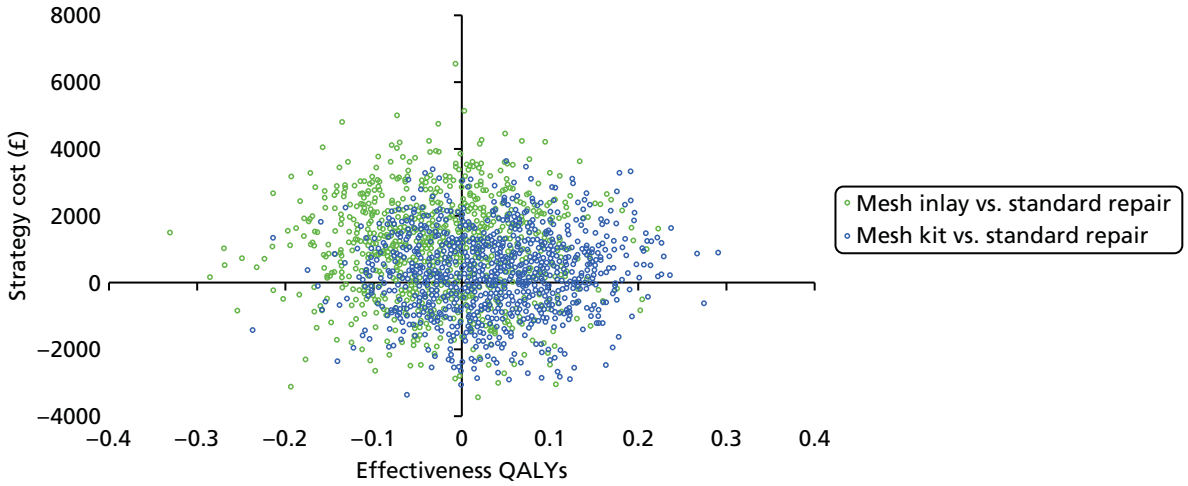


FIGURE 24 Scatterplot of incremental wider economic costs and QALYs for mesh treatments compared with standard repair – secondary prolapse repair (2-year follow-up).

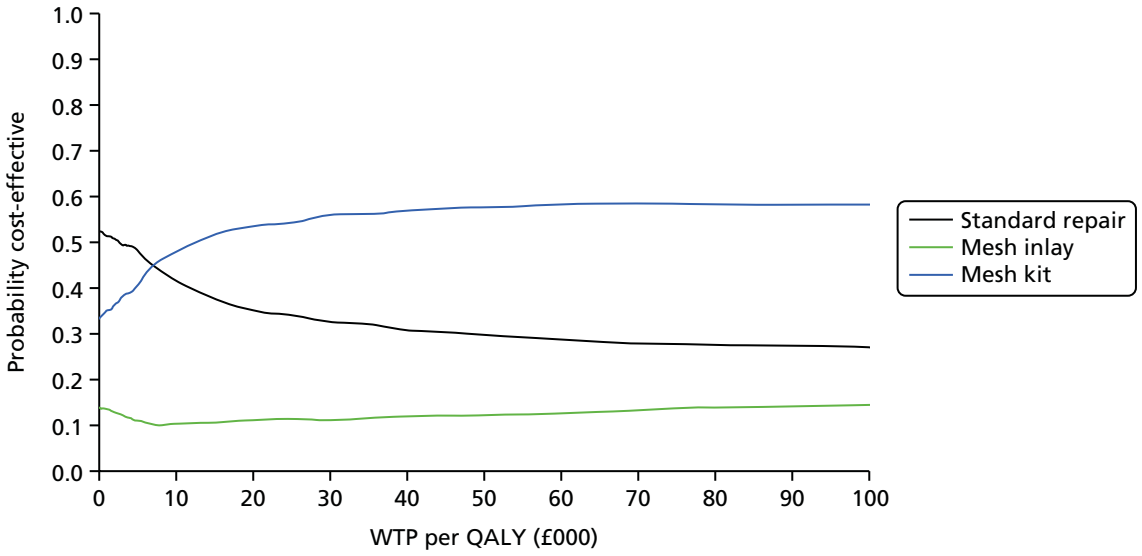


FIGURE 25 Cost-effectiveness acceptability curves: Secondary trial – 2-year follow-up, wider economic perspective.

Deterministic sensitivity analyses

As demonstrated in the CEACs and scatterplots presented in this chapter for the Secondary trial analysis, there is substantial uncertainty driven by the small sample size of women randomised to the secondary comparison. Although CEACs and scatterplots based on bootstrapped iterations are important in presenting sampling uncertainty, they do not consider the impact of missing data, methodological assumptions such as the discount rate or the choice of comparison used in the analysis.

A number of sensitivity analyses were carried out as described in the *Chapter 2* to assess the uncertainty in our results to these data choices and assumptions. Complete cost data at 2 years of follow-up were used for the sensitivity analyses. We explored a gamma family, log link regression model for costs, as both this and a normal distribution passed the modified Park's test for distributional family. Furthermore, both models had similar AIC values, with the normal distribution having only a slightly lower score, hence its choice for the base-case analysis. However, the conclusions remain broadly robust to the choice of analysis model for the data.

Our results were also consistent across alternative discount rates applied to costs and QALYs in the second year. Overall, the ranking of treatment options based on the net benefit statistic (at a threshold value of WTP of £30,000 per QALY gained) remained unchanged for the exploration of alternative discount rates and analysis model, with mesh kits and standard repairs being slightly preferred over mesh inlay.

The base case was conducted for all women randomised to the Secondary trial. The approach differed to the primary economic analysis, as it was felt that because of the small sample size, the trade-offs of presenting a three-way comparison were outweighed by the advantages of increasing the power of the analysis as much as possible. However, we also explore the impact of re-running the analysis for the Secondary trial using data provided by only those women who were randomised to the three-way comparison (RCT2A). The choice of comparison for the data analysis was found to impact on the treatment rankings, with standard repair having the highest probability of cost-effectiveness for this analysis. However, as with all other analyses, no one treatment strategy was clearly cost-effective and substantial uncertainty surrounding estimates was illustrated.

Missing data

Missing data are likely to be particularly important for the secondary comparison given the limited sample, for which even small differences between numbers of women with missing data between groups can have a large impact on outcomes. It was not possible to impute individual resource-use item data for every category of costs, given that the number of parameters was greater than the number of observations for some imputed parameters. Therefore, imputation was undertaken at a total cost level. QALYs were based on calculation of imputed EQ-5D-3L scores at 6 months, 1 year and 2 years. The point estimates from the regressions of incremental costs and QALYs remain broadly unchanged for the comparison of mesh kit compared with standard repair. However, point estimates become more favourable to the mesh inlay comparison under the assumptions of the imputed data set. On first impression, this seems like a substantial difference in conclusions; however, when considering the width of the CIs, the conclusion that there is no evidence of any difference between the groups remains unchanged (both in terms of costs to the NHS and QALYs gained). Considering the assessment of sampling uncertainty for the imputed data set, the probability of cost-effectiveness at a threshold value of WTP for a QALY gained for each strategy is as follows: standard repair (14%), mesh inlay (56%) and mesh kit (30%). These probabilities compare with 32%, 19% and 49%, respectively, for each of the three strategies that were estimated in the base-case analysis. The probability of cost-effectiveness is higher for mesh inlay under the assumptions of the imputed data set. However, again, substantial uncertainty exists with no strategy presenting a probability of cost-effectiveness of > 60%.

The results across all of the deterministic sensitivity analyses and imputation models undertaken for the Secondary trial comparison are presented in *Table 76*. Data on the right-hand side of the table present the probability of cost-effectiveness of each strategy for each analysis undertaken, based on the net benefit statistic, for a £30,000 ceiling ratio of a decision-maker's WTP for a QALY gained.

Across all of the analyses undertaken, as with the base-case analysis, there was substantial uncertainty in all the estimates of incremental costs, incremental QALYs and ICERs. Conclusions should be drawn in the light of this uncertainty and not necessarily on the point estimates of the ICERs presented, which, as a result of the very wide CIs, were found to be quite unstable. In summary, there is no clear evidence that any one treatment is particularly cost-effective for the surgical repair of secondary prolapse. This conclusion was consistent across alternative analyses. There was some further uncertainty, however, regarding cost-effectiveness, depending on whether imputed data were used or not. However, across all analyses explored, none of the treatment options has a probability of cost-effectiveness of > 60% if decision-makers were willing to pay a maximum of £30,000 per QALY gained. Therefore, substantial sampling uncertainty remained for all of the analyses considered. Further research, over a longer time horizon is required to determine the long-run trade-offs between costs and QALYs, which will probably be driven primarily by any differences that may emerge over the longer-term in risk of complications and risk of prolapse surgery failure.

TABLE 76 Deterministic sensitivity analyses undertaken for trial-based cost-effectiveness analysis: secondary prolapse repair

	Costs (£)[a]			QALYs[a]			Incremental cost (£)		Incremental QALYs		ICER (£/QALY)		P(CE) @WTP = £30,000/QALY gain[b]		
Analysis	Standard repair	Mesh inlay	Mesh kit	Standard repair	Mesh inlay	Mesh kit	Mesh inlay vs. standard repair: MD (95% CI)	Mesh kit vs. standard repair: MD (95% CI)	Mesh inlay vs. standard repair: MD (95% CI)	Mesh kit vs. standard repair: MD (95% CI)	Mesh inlay vs. standard repair	MK vs. standard repair	Standard repair	Mesh inlay	Mesh kit
Base case	3883	4133	4528	1.486	1.600	1.614	236 (–1091 to 1564)	642 (–309 to 1592)	–0.023 (–0.163 to 0.118)	0.050 (–0.085 to 0.185)	Dominated	11,560	0.32	0.19	0.49
Costs and QALYs undiscounted	3903	4152	4546	1.512	1.628	1.643	231 (–1107 to 1569)	636 (–324 to 1596)	–0.023 (–0.166 to 0.120)	0.052 (–0.085 to 0.190)	Dominated	10,904	0.33	0.17	0.51
Costs and QALYs discounted at 6% per annum	3870	4121	4515	1.468	1.581	1.594	241 (–1116 to 1599)	379 (–541 to 1299)	–0.023 (–0.161 to 0.116)	0.056 (–0.076 to 0.188)	Dominated	6,768	0.32	0.20	0.48
Data from three-way comparison (RCT2A) only	3590	4044	4586	1.667	1.597	1.610	–391 (–1707 to 943)	413 (–597 to 1413)	–0.040 (–0.234 to 0.154)	–0.017 (–0.153 to 0.120)	9775[c]	Dominated	0.47	0.32	0.20
Multiple imputation of missing cost and QALY data	4016	3933	4639	1.530	1.605	1.578	–83 (–1071 to 904)	623 (–474 to 1719)	0.074 (–0.055 to 0.204)	0.048 (–0.101 to 0.196)	Dominant	12,979	0.14	0.56	0.30
Gamma regression of cost, log link	3886	4191	4657	1.486	1.560	1.614	222 (–1202 to 1645)	613 (–456 to 1682)	–0.023 (–0.163 to 0.118)	0.050 (–0.085 to 0.185)	Dominated	12,260	0.37	0.15	0.49

a Costs and QALYs incurred during the second year are discounted at a rate of 3.5% per annum for all of the analyses unless otherwise stated.
b 'P(CE) @WTP = £30,000/QALY gain' represents the probability that each intervention is cost-effective, based on the net benefit statistic, if a decision-maker were willing to pay £30,000 for one QALY gained.
c The ICER presented of £9775 is interpreted as the incremental cost savings per QALY lost, and differs from the other positive ICER interpretations.
All of the analyses are based on 2-year costs and outcomes.

Discussion

Summary of main findings

For the base-case economic analysis of mesh inlays and mesh kits compared with standard repair for women requiring a secondary prolapse surgery procedure, there is evidence to suggest that mesh kits are substantially more expensive as a result of the additional cost of materials over and above standard repairs and, indeed, mesh inlays. There were no differences, however, in costs of time or equipment to perform the respective procedures, nor were there any differences evident in terms of follow-up care required across groups. There was no strong evidence that either mesh strategy provides QALY gains relative to standard repair. It should be noted that point estimates of incremental costs, incremental QALYs and hence incremental cost per QALY gained were surrounded by very wide CIs, illustrating the uncertainty surrounding the estimates. This is primarily due to a small sample size and a lack of power to estimate cost-effectiveness outcomes. As such, point estimates of the estimated ICER should be interpreted with extreme caution and in the light of the uncertainty surrounding these estimates. The best way to interpret the estimates of cost-effectiveness in the light of this uncertainty is to consider the data presented in scatterplots of incremental costs and QALYs gained and the CEACs presented. The latter suggest that, were society willing to pay up to £30,000 for a QALY gain, there are probabilities of 32%, 19% and 49% that standard repair, mesh inlays and mesh kits, respectively, are the optimal treatment strategy from a cost-effectiveness point of view. These probabilities clearly illustrate great uncertainty regarding the most cost-effective strategy. Similarly, uncertain estimates are presented for all of the deterministic sensitivity analyses undertaken and also for the exploratory imputation of missing data. Under none of the circumstances considered would any one treatment option represent a > 60% probability of being the most cost-effective option. Under these uncertain estimates, there is no evidence to draw conclusions regarding cost-effectiveness of any of the treatment options considered for secondary prolapse repair on the basis of 2-year follow-up data.

Strengths

Despite the uncertainty and the small sample size for this trial, the data presented are the only data available specifically in relation to costs and QALYs for women experiencing a secondary prolapse repair. Furthermore, the sample, although small, is the largest trial and body of evidence considered to date for secondary repairs. By following these women up over a longer time, it will be possible to gain a better picture of the longer-term trade-offs between complications and recurrences, which will probably have a heavy impact on longer-term cost-effectiveness estimates.

As with the Primary trial, a key strength of the study was the UK-wide multicentre design randomising women from 35 centres across the UK. This adds to the external validity and generalisability of the results UK-wide. Including a full within-trial cost-effectiveness analysis is a key strength, although data may be of limited value in determining longer-term cost-effectiveness results. The main strength from the within-trial analysis is that a comprehensive microcosting approach was undertaken, further adding to the generalisability of results across participating centres.

The incorporation of a wider economic perspective on costs as a secondary analysis adds value in terms of providing initial indications of the costs to women and economic costs to society of secondary prolapse symptoms and problems. The estimates generated from the time and travel cost estimates can be applied in future studies of prolapse repair, to expand the perspective of the analysis. The analysis of QALYs, based on EQ-5D-3L patient-level responses, follows best practice methods; this is another advantage, which will be useful for any future modelling exercises of secondary prolapse repair. For the purposes of this evaluation, there are insufficient numbers of observations with long enough follow-up to accurately project time to effect analysis to populate a decision-analytic model specifically for secondary prolapse repair. However, once longer-term data are available, this will be possible and thus forms a part of the longer-term plan for this project.

Limitations

The main limitation of the Secondary trial economic analysis is the small sample size available for analysis. This greatly limits the statistical power of the analysis and limits the interpretation of the results presented because of the wide CIs and unstable point estimates of incremental costs, incremental QALYs and hence ICERs.

Furthermore, as with the Primary trial, we have conducted a microcosting approach to develop intervention costs, based on data available from the trial, supplemented by contact with trial-participating surgeons to glean information on mesh materials used to conduct prolapse repairs. Although the microcosting is an advantage, it has also generated some limitations. First, the estimates of mesh costs are based on average prices across mesh categories and we make no statements about the cost-effectiveness of individual mesh products. This is an area requiring future research to determine if individual products provide better outcomes and more cost-effective treatment options for women. Second, the data are presented for average practice for each surgeon, and are not available at an individual patient level for all of the women participating in the trial.

For the Secondary trial data analysis, we have chosen to include all women who were randomised, not just those who were randomised to the three-way comparison, as we did for the Primary trial. From a cost-effectiveness perspective, sourcing data for net benefit calculations from the three-way comparison is the preferable approach to take. However, in this case, because of the small randomised sample for the Secondary trial, the advantages of a straight 'purist' three-way comparison are outweighed by the disadvantages of a substantial loss in already limited statistical power. Readers should note the potential limitations of this approach for cost-effectiveness analysis in a net benefit framework.

There were some missing data for cost and QALY outcomes, which are particularly problematic given the small sample size. Exploratory imputations of missing total cost and EQ-5D data were conducted, indicating wide variability in ICERs presented, although a consideration of uncertainty and the CEACs presented broadly similar results to the base-case analysis.

Furthermore, it should be noted that this short time horizon provides a further limitation, as it fails to address the cost and QoL impacts of any long-term complications or treatment failures, and any differences in time to failure/time to experiencing serious complications following initial surgery.

Conclusions

There was no clear evidence of the most cost-effective treatment strategy for secondary prolapse repair. Estimates of ICERs and cost-effectiveness were highly uncertain and should be interpreted in light of this uncertainty and the limitations outlined. It is unlikely that a 2-year follow-up is of sufficient duration to capture all of the costs and QALYs that are of importance to women and the NHS, and hence longer-term follow-up of the PROSPECT Study will be used to update the cost-effectiveness results. This will also provide an opportunity to develop more robust methods of extrapolation over a lifetime, which will enable the development of a longer-term decision-analytic model specifically for secondary prolapse repair. Unfortunately, as a result of the small sample size, there are insufficient data to develop robust or stable models of time-to-event data to develop an economic model at this time for secondary prolapse repair. Extended follow-up to 6 years will be used to rerun the cost-effectiveness analyses for secondary repairs and provide better cost-effectiveness evidence. Furthermore, longer-term data will provide more accurate estimates of failures and complications and provide an opportunity to build a model for secondary prolapse repair.

Chapter 8 Results upper compartment: uterine and vault prolapse (comprehensive cohort 3)

This chapter describes the women who, when assessed clinically before surgery, were not thought to need an anterior or posterior prolapse repair. If they had, they would have been eligible for randomisation in the mesh trials (see *Chapters 4* and *5*). These women had an upper compartment (uterine or vault) procedure and agreed to be followed up as part of the CC (CC3).

The flow of women through the study is shown in the CONSORT diagram (*Figure 26*). The women received surgery in centres across the UK (see *Table 4*). Although 215 women had uterine or vault surgery in total,

Type of repair	Uterine/vault 215		
Treatment arm	CC3 *n* = 251	Uterine *n* = 69	Vault *n* = 146
	Received surgery *n* = 212 (99%)	Received surgery *n* = 68 (99%)	Received surgery *n* = 144 (99%)
Standard repair	*n* = 17 (8%)	*n* = 12 (18%)	*n* = 5 (3%)
Synthetic mesh	*n* = 3 (1%)	*n* = 0 (0%)	*n* = 3 (2%)
Biological graft	*n* = 0 (0%)	*n* = 0 (0%)	*n* = 0 (0%)
Mesh kit	*n* = 1 (0%)	*n* = 0 (0%)	*n* = 1 (1%)
Other surgery	*n* = 191 (90%)	*n* = 56 (82%)	*n* = 135 (94%)
No surgery	*n* = 3 (1%)	*n* = 1 (1%)	*n* = 2 (1%)
Baseline questionnaire	*n* = 202 (94%)	*n* = 65 (94%)	*n* = 137 (94%)
6-month questionnaire	*n* = 175 (83%)	*n* = 54 (79%)	*n* = 121 (84%)
Withdrawals within 6 months	*n* = 1 (0%)	*n* = 0 (0%)	*n* = 1 (1%)
Deaths within 6 months	*n* = 1 (0%)	*n* = 0 (0%)	*n* = 1 (1%)
12-month short questionnaire	*n* = 173 (82%)	*n* = 57 (84%)	*n* = 116 (81%)
12-month long questionnaire	*n* = 158 (75%)	*n* = 46 (68%)	*n* = 112 (78%)
12-month clinic assessment	*n* = 0 (0%)	*n* = 0 (0%)	*n* = 0 (0%)
Withdrawals within 12 months	*n* = 5 (2%)	*n* = 1 (1%)	*n* = 4 (3%)
Deaths within 12 months	*n* = 1 (0%)	*n* = 0 (0%)	*n* = 1 (1%)
24-month questionnaire	*n* = 152 (72%)	*n* = 48 (71%)	*n* = 104 (72%)
Withdrawals within 24 months	*n* = 11 (5%)	*n* = 3 (4%)	*n* = 8 (6%)
Deaths within 24 months	*n* = 4 (2%)	*n* = 2 (3%)	*n* = 2 (1%)

FIGURE 26 CONSORT diagram for uterine and vault groups.

they have been reported separately because of the fundamental clinical differences between them. The most important difference is that women who have a vault prolapse must have had a hysterectomy in the past. Therefore, in this chapter, the data are presented according to clinical presentation, statistical comparisons are not made between the groups and the information is presented and discussed separately.

It is important to realise that the total number of women in CC3 is not representative of the distribution of uterine and vault prolapse in the UK. There are an artificially high number of women who were having vault prolapse because several of the PROSPECT centres were tertiary referral centres for vault prolapse or specialised in its laparoscopic treatment. The true ratio of uterine–vault prolapse is around 4 : 1, suggesting that one in four women who have a hysterectomy go on to have a subsequent vault prolapse repair. These numbers are in line with Health Episode Statistics (HES) data, which suggest that 25% of women who were having a hysterectomy will go on to require a vault repair.[6]

Interestingly, although most (but not all) vaginal hysterectomies are carried out for prolapse and most (but not all) abdominal hysterectomies for other gynaecological conditions, the number of women with prolapse was marginally greater after an abdominal hysterectomy (543/961, 56.5%) than after a vaginal hysterectomy (418/961, 43.5%; see *Table 5*). This must be set against the much higher number of women who were having an abdominal hysterectomy in the past (e.g. > 31,000 women who were having an abdominal hysterectomy compared with around 6500 having a vaginal hysterectomy in 2004–5).[6]

Overall, around 25% of women who were having a uterine prolapse repair can expect to have a vault repair later.[6] This information is derived from online HES data, and so may underestimate total procedures, as it was based only on numbers of main operations and therefore did not count concomitant procedures.

Baseline characteristics of women who were having a uterine or a vault prolapse repair

Women who were having surgery for a uterine prolapse were, on average, 5.6 years younger than those having a vault repair (*Table 77*). However, compared with women who were having a uterine prolapse repair, women who were having a vault repair had a higher prolapse symptom score (POP-SS of 15.3 vs. 12.8); higher score on QoL (7.3 vs. 6.5); worse generic QoL score (EQ-5D-3L score of 0.63 vs. 0.69); more severe incontinence (23.8% vs. 21%) and prior surgery for UI (16.8% vs. 7.4%) and were more likely to have had prolapse surgery before (57.5% vs. 14.5%). They were less likely to be currently using a pessary (11.8% vs. 15.9%) or to have received physiotherapy for their prolapse symptoms (27.5% vs. 34.3%).

Although not all of these differences were statistically significant, together they provide an impression of the qualitative differences between the populations of women with the two types of prolapse: this supports our decision not to combine or directly compare the data from the two groups. Thus, in summary, women who were having vault prolapse surgery were older, had more severe symptoms and had received more invasive treatment than those presenting with a uterine prolapse alone. For that reason, the two samples of women will be described separately in the rest of this chapter.

Uterine prolapse: women requiring a prolapse repair for descent of the uterus only

Women's characteristics at baseline

The mean age of women presenting with a uterine prolapse alone was 56.9 years (see *Table 77*). This is considerably younger than the other groups of women in PROSPECT, including those with a primary or secondary anterior or posterior prolapse (see *Table 5*) or a vault prolapse (see *Table 77*). However, the groups were generally all comparable on other characteristics such as parity, BMI and delivery mode history.

TABLE 77 Baseline characteristics: uterine/vault cohort (CC3)

Baseline characteristic	Uterine			Vault		
Number of women	*N* = 69			*N* = 146		
Age (years)	56.9	(15.2)	69	62.5	(10.1)	146
Parity (mean)	2.6	(1.4)	69	2.8	(1.4)	146
Parity (median)	2.0	(0–7)	69	3.0	(0–12)	146
BMI (kg/m^2) (mean)	27.4	(4.3)	64	27.1	(4.3)	138
BMI (kg/m^2) (median)	27.8	(19–36)	64	26.6	(19–40)	138
Delivery mode history						
Spontaneous vaginal delivery	2.3	(1.5)	68	2.6	(1.5)	143
Forceps	0.2	(0.4)	68	0.1	(0.4)	143
Breech	0.0	(0.0)	68	0.1	(0.3)	143
Elective CS	0.0	(0.2)	68	0.0	(0.2)	143
Emergency CS	0.0	(0.0)	68	0.0	(0.1)	143
Vacuum	0.0	(0.0)	68	0.0	(0.1)	143
EQ-5D-3L						
Score	0.69	(0.30)	60	0.63	(0.34)	129
Conservative treatment						
Vaginal pessary	15.9%	11	69	11.8%	17	144
Physiotherapy for POP	34.3%	23	67	27.5%	39	142
Physiotherapy for UI	17.9%	12	67	17.7%	25	141
Drugs for UI	7.7%	5	65	12.1%	17	140
Previous surgery						
Hysterectomy	0.0%	0	69	100.0%	146	146
Vaginal	0.0%	0	69	47.3%	69	146
Cervical amputation	2.9%	2	69	2.1%	3	146
Abdominal	0.0%	0	69	51.4%	75	146
UI surgery	7.4%	5	68	16.8%	24	143
Prolapse repair	14.5%	10	69	57.5%	84	146
Anterior	10.1%	7	69	34.2%	50	146
Posterior	5.8%	4	69	25.3%	37	146
Anterior plus posterior	4.3%	3	69	17.1%	25	146
Vault	2.9%	2	69	15.8%	23	146
Unknown	1.4%	1	69	4.1%	6	146

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

About one-third of the women with a uterine prolapse had seen a physiotherapist for prolapse, and about one in eight had used a pessary for prolapse symptoms (see *Table 77*). One in five women had seen a physiotherapist for urine symptoms and fewer than 1 in 10 had used drugs for urinary problems.

Preoperative prolapse measurements

The leading edge of the upper compartment (point C on the POP-Q) was, on average, at or beyond the hymen (1.7 cm for uterine prolapse; *Table 78*). The majority of women had stage 3 or 4 prolapse, unlike those having only an anterior or posterior repair, for which the most common preoperative stage was

TABLE 78 Preoperative objective measures of prolapse: uterine/vault cohort (CC3)

POP-Q measurement/stage	Uterine			Vault		
Number of women	*N* = 69			*N* = 146		
POP-Q measurement (cm)						
Ba (anterior edge)	2.0	(2.3)	60	2.0	(2.4)	133
C (cervix/vault)	1.7	(3.1)	51	–0.4	(3.9)	133
Bp (posterior edge)	0.2	(2.9)	59	0.9	(2.6)	133
TVL	8.5	(1.3)	51	8.4	(1.9)	108
Overall POP-Q stage						
0	0.0%	0	64	0.0%	0	139
1	4.7%	3	64	0.0%	0	139
2	37.5%	24	64	37.4%	52	139
3	43.8%	28	64	48.9%	68	139
4	14.1%	9	64	13.7%	19	139
2b, 3 or 4	*77.0%*	*47*	*61*	*84.3%*	*113*	*134*

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Prolapse
Ba, the leading edge of the anterior vaginal wall; Bp, the leading edge of the posterior vaginal wall; C, the leading edge of the uterus/vault.

stage 2 (see *Table 7*). Using a more strict definition of prolapse (leading edge > 0 cm beyond the hymen), 77.0% of women had a prolapse beyond the hymen.

Prolapse symptoms at baseline

All women had at least one prolapse symptom on the Pelvic Organ Prolapse Symptom scale, the most common of which was 'a feeling of something coming down from or in (your) vagina' (*Table 79*). Women who were having a uterine prolapse repair had a lower prolapse symptom score (POP-SS of 12.8) and less bother from their prolapse, based on their prolapse-related QoL score (6.5) than women who were having anterior or posterior repair (see *Tables 15* and *50*) or vault repair (see *Table 79*). The principal individual prolapse symptom was a feeling of 'something coming down'. They were also less likely to need to use preventative manoeuvres or extra hygiene measures to relieve their prolapse and other symptoms of pelvic floor dysfunction.

TABLE 79 Prolapse symptoms at baseline: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women	***N* = 65**			***N* = 137**		
POP-SS overall	12.8	(6.3)	61	15.3	(6.6)	136
Individual prolapse symptoms						
SCD any	98.4%	60	61	96.3%	131	136
SCD freq.	70.5%	43	61	80.9%	110	136
Pain any	83.6%	51	61	86.8%	118	136
Pain freq.	31.1%	19	61	55.1%	75	136
Abdo. any	75.4%	46	61	82.4%	112	136
Abdo. freq.	26.2%	16	61	39.0%	53	136
Back any	62.3%	38	61	74.3%	101	136
Back freq.	31.1%	19	61	27.9%	38	136

TABLE 79 Prolapse symptoms at baseline: uterine/vault cohort (CC3) (*continued*)

Symptom	Uterine			Vault		
Strain blad. any	59.0%	36	61	73.5%	100	136
Strain blad. freq.	27.9%	17	61	34.6%	47	136
Blad. not empty any	82.0%	50	61	85.3%	116	136
Blad. not empty freq.	32.8%	20	61	42.6%	58	136
Bowel not empty any	68.9%	42	61	85.3%	116	136
Bowel not empty freq.	24.6%	15	61	33.8%	46	136
Other measures of prolapse symptoms						
Symptoms (years)	5.2	(6.3)	57	3.9	(4.5)	127
Bother (years)	3.2	(3.4)	55	3.2	(3.8)	122
Number of women symptomatic	100.0%	61	61	100.0%	136	136
Prolapse-related QoL score	6.5	(3.0)	61	7.3	(2.8)	132
Actions necessitated by prolapse symptoms						
Fingers to ease discomfort	17.5%	11	63	33.3%	42	126
Extra hygiene measures	49.2%	30	61	63.4%	83	131
Fingers to help empty bladder	8.2%	5	61	12.4%	16	129
Fingers to help empty bowel	1.6%	1	62	6.2%	8	130
Digital evacuation of bowel	3.2%	2	63	5.3%	7	133

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Individual prolapse symptoms

Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time.; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely? (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad.* any: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.

Prolapse

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome; *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

Actions necessitated by prolapse symptoms

Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

Urinary symptoms at baseline

Based on a variety of validated measures of assessing bladder function, women with uterine prolapse were similar to the other groups of women who were having prolapse surgery on nearly every measure. In particular, UI was just as prevalent, four in five women had any incontinence, and one in five had severe symptoms (*Table 80*).

TABLE 80 Urinary symptoms at baseline: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women	*N* = 65			*N* = 137		
Any incontinence	77.8%	49	63	73.7%	98	133
ICIQ-UI-SF score	7.1	(5.8)	62	7.1	(6.1)	130
Severe incontinence	21.0%	13	62	23.8%	31	130
Incontinence QoL	3.8	(3.6)	57	3.8	(3.6)	124
Stress UI	21.4%	12	56	22.6%	26	115
Urgency UI	9.5%	6	63	13.0%	17	131
Overactive bladder	6.3%	4	63	7.8%	10	129
ICIQ-FLUTS filling score	5.0	(3.1)	62	6.0	(3.1)	127
ICIQ-FLUTS voiding score	3.4	(2.8)	62	3.4	(2.7)	130
ICIQ-FLUTS incontinence score	5.5	(4.1)	56	5.8	(4.3)	113

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Urinary symptoms
Any incontinence: Defined as 'How often do you leak urine? (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

Bowel symptoms at baseline

Women with uterine prolapse were similar with respect to most aspects of bowel function to those with other types of prolapse. At least one-fifth had constipation and almost one-third had FI (*Table 81*). Passive FI was much more common than active (FI accompanied by bowel urgency).

Vaginal and sexual symptoms at baseline

About two in five women were sexually active (*Table 82*). For those who did have a partner, the most common reason for no sex life was their prolapse symptoms. Very few of the women (3.1%) had dyspareunia (pain with intercourse) but the numbers were small.

Planned surgery and surgery actually carried out

Planned surgery

To be enrolled in CC3, women were clinically assessed as not needing an anterior or posterior repair. Only three women were thought to need continence surgery (despite > 20% having severe UI; *Table 83*).

Surgery actually received

Although the women in this cohort were thought to have a uterine prolapse, only around 30% had a vaginal hysterectomy. A total of 14.7% of uterine women had a hysterectomy with a concomitant vault repair (see *Table 83*).

TABLE 81 Bowel symptoms at baseline: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women	*N* = 65			*N* = 137		
Bowel frequency						
> 3 times a day	3.3%	2	61	5.2%	7	134
1–3 times a day	34.4%	21	61	31.3%	42	134
About once a day	34.4%	21	61	41.0%	55	134
Once every 2–3 days	21.3%	13	61	19.4%	26	134
Weekly or less	6.6%	4	61	3.0%	4	134
Constipation	21.0%	13	62	25.4%	33	130
Bowel urgency	7.9%	5	63	11.9%	16	134
Any FI	31.7%	20	63	32.6%	43	132
Passive FI	75.0%	15	20	69.8%	30	43
Active FI	25.0%	5	20	30.2%	13	43
Severe FI	4.8%	3	63	11.4%	15	132
Bowel symptoms QoL	2.9	(3.3)	62	3.4	(3.3)	133

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Bowel symptoms
Active faecal incontinence: Any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

Description of surgical characteristics and protocols

The majority of women with a uterine prolapse received surgery from a consultant gynaecologist (70.6%); junior doctors were supervised in > 90% of cases *(Table 84*). Most women had a general anaesthetic, received prophylactic antibiotics and were in theatre for approximately 2 hours. The mean length of stay was > 2 days.

Outcomes for women who were having a uterine prolapse repair

Serious and related adverse effects in first and second years

The proportion of women who had at least one serious adverse effect in the first year (excluding mesh complications) was 4.3% in the uterine group (three women had seven events; *Table 85*). One woman had urinary tract symptoms in the second year. Five women also had at least one non-serious adverse event in the first year (excluding mesh complications; *Table 86*).

Prolapse symptoms and EuroQol-5 Dimensions (3-level version)

At 6 months, the women's report of their prolapse symptoms, using the POP-SS (maximum score 28), fell from 12.8 (see *Table 79*) for the uterine group to 4.3 (*Table 87*). Similarly, each individual prolapse symptom also improved (*Table 88*), as did the prolapse-related QoL scores (*Table 87*).

TABLE 82 Vaginal and sexual symptoms at baseline: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women	*n* = 65			*n* = 137		
Vaginal						
ICIQ-VS score	23.6	(9.6)	56	24.5	(10.4)	115
Vaginal symptoms QoL score	5.1	(3.5)	59	5.4	(3.6)	128
Vagina too tight	3.3%	2	60	3.2%	4	125
Sexual						
Sex life at present (yes)	41.0%	25	61	32.8%	44	134
Reason for no sex life						
No partner	44.4%	16	36	32.2%	29	90
Vaginal symptoms	5.6%	2	36	2.2%	2	90
Prolapse symptoms	36.1%	13	36	46.7%	42	90
Other reason	8.3%	3	36	14.4%	13	90
Reason not given	5.6%	2	36	4.4%	4	90
Dyspareunia	3.1%	1	32	14.8%	9	61
Sexual Matters Score	21.1	(14.1)	30	24.4	(15.5)	59
Sex life QoL score	6.4	(3.5)	37	6.9	(3.4)	77

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Vaginal and sexual symptoms
Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *Dyspareunia at baseline*: denominator includes number of women who were sexually active and those who did not have a sex life because of prolapse symptoms. *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight? (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

At 1 year, this improvement was maintained (POP-SS of 5.2 for the uterine group; see *Table 87*). The improvement from baseline was supported by data from individual prolapse symptoms (measured as occurring 'ever' or 'most or all of the time'); the proportion of women who had at least one prolapse symptom ('symptomatic'); QoL data based on the interference of prolapse symptoms on everyday life; the generic QoL measure EQ-5D-3L; and the need to undertake extra hygiene measures or manoeuvres to assist pelvic floor functions (see *Tables 88* and *89*). All of these measures demonstrated significant improvements from before surgery.

The improvement at 1 year was maintained at 2 years, with respect to all the prolapse outcomes and QoL outcomes measured.

Urinary symptoms

Detailed information on urinary symptoms was obtained at baseline, 1 year and 2 years (see *Tables 80* and *90*). The number of women who had concomitant continence surgery was 3 of 69 in the uterine group (see *Table 83*).

At 1 year in the uterine group, the proportion of women who had any UI decreased from 77.8% to 65.2% (see *Tables 80* and *90*), and the proportion with severe UI more than halved (from 21% to 6.7%). There were similar moderate improvements in all the other measures of bladder function measured.

TABLE 83 Planned surgery and surgery actually carried out: uterine/vault cohort (CC3)

Type of surgery	Uterine			Vault		
Number of women	*N* = 69			*N* = 146		
Planned prolapse surgery						
Anterior repair	0.0%	0	69	0.0%	0	146
Posterior repair	0.0%	0	69	0.0%	0	146
Anterior and posterior repair	0.0%	0	69	0.0%	0	146
Upper compartment repair only	100.0%	69	69	100.0%	146	146
Concomitant prolapse surgery						
Vaginal hysterectomy	31.9%	22	69	0.0%	0	146
Abdominal hysterectomy	5.8%	4	69	0.7%	1	146
Cervical amputation	4.3%	3	69	0.7%	1	146
Vault repair	72.5%	50	69	99.3%	145	146
Concomitant UI surgery	4.3%	3	69	4.1%	6	146
Surgery actually received						
Anterior repair only	10.3%	7	68	2.8%	4	144
Posterior repair only	4.4%	3	68	1.4%	2	144
Anterior and posterior repair	2.9%	2	68	2.1%	3	144
Neither	82.4%	56	68	93.8%	135	144
Vaginal hysterectomy	29.4%	20	68	0.0%	0	144
Vault repair	14.7%	10	68	89.6%	129	144
Continence surgery	4.4%	3	68	3.5%	5	144

Dichotomous variables are presented as '% *n N*'.

TABLE 84 Description of surgical characteristics and protocols: uterine/vault cohort (CC3)

Surgical characteristic	Uterine			Vault		
Number of women	*N* = 68			*N* = 144		
Grade of gynaecologist						
Consultant	70.6%	48	68	78.3%	112	143
Specialty doctor		0	68	1.4%	2	143
Specialty doctor supervised	N/A	0	0	100.0%	2	2
Registrar/junior	29.4%	20	68	20.3%	29	143
Specialty doctor supervised	94.4%	17	18	89.7%	26	29
Type of anaesthetic						
General	86.8%	59	68	93.7%	134	143
Spinal	14.7%	10	68	6.3%	9	143
Local	1.5%	1	68	5.6%	8	143
Prophylactic antibiotic	92.6%	63	68	98.6%	139	141
Estimated blood loss (ml)	246.9	(353.6)	54	52.9	(62.7)	106

continued

TABLE 84 Description of surgical characteristics and protocols: uterine/vault cohort (CC3) (*continued*)

Surgical characteristic	Uterine			Vault		
Duration (minutes)	121.8	(44.1)	67	131.9	(47.2)	142
Vaginal pack inserted	51.5%	34	66	15.7%	22	140
Catheter inserted	98.5%	65	66	99.3%	142	143
Suprapubic	1.5%	1	65	1.4%	2	142
Urethral	98.5%	64	65	98.6%	140	142
Both	0.0%	0	65	0.0%	0	142
Length of stay (days)	2.4	(3.3)	68	1.8	(1.5)	143

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

TABLE 85 Serious and related adverse effects in years 1 and 2: uterine/vault cohort (CC3)

Adverse effect	Uterine			Vault		
Number of women in first year	*N* = 69			*N* = 146		
Intraoperative						
Injury to organs	0.0%	0	69	0.7%	1	146
Excess blood loss	1.4%	1	69	0.0%	0	146
Blood transfusion	2.9%	2	69	0.0%	0	146
Anaesthetic complications	0.0%	0	69	0.7%	1	146
Death	0.0%	0	69	0.0%	0	146
Postoperative						
Thrombosis	0.0%	0	69	0.0%	0	146
Infection	1.4%	1	69	0.0%	0	146
Pain	0.0%	0	69	0.7%	1	146
Urinary retention	0.0%	0	69	0.0%	0	146
Bowel obstruction	0.0%	0	69	0.7%	1	146
Constipation	1.4%	1	69	0.0%	0	146
Excess blood loss	2.9%	2	69	0.0%	0	146
Vaginal adhesions	0.0%	0	69	0.0%	0	146
Haematoma	0.0%	0	69	0.0%	0	146
Skin tags	0.0%	0	69	0.0%	0	146
Granulation tissue	0.0%	0	69	0.0%	0	146
Urinary tract symptoms	0.0%	0	69	0.0%	0	146
Death	0.0%	0	69	0.0%	0	146
Number of women with any serious complication in first year	*4.3%*	*3*	*69*	*2.7%*	*4*	*146*
Number of women in second year	*N* = 69			*N* = 146		
Thrombosis	0.0%	0	69	0.0%	0	146
Infection	0.0%	0	69	0.7%	1	146

TABLE 85 Serious and related adverse effects in years 1 and 2: uterine/vault cohort (CC3) (*continued*)

Adverse effect	Uterine			Vault		
Pain	0.0%	0	69	0.7%	1	146
Urinary retention	0.0%	0	69	0.0%	0	146
Bowel obstruction	0.0%	0	69	0.0%	0	146
Constipation	0.0%	0	69	0.0%	0	146
Excess blood loss	0.0%	0	69	0.0%	0	146
Vaginal adhesions	0.0%	0	69	0.0%	0	146
Haematoma	0.0%	0	69	0.0%	0	146
Skin tags	0.0%	0	69	0.0%	0	146
Granulation tissue	0.0%	0	69	0.0%	0	146
Urinary tract symptoms	1.4%	1	69	0.0%	0	146
Death	0.0%	0	69	0.0%	0	146
Number of women with any serious complication in second year	*1.4%*	*1*	*69*	*0.7%*	*1*	*146*

N/A, not applicable.
Dichotomous variables are presented as '% *n N*'.
Serious: Causing death, requiring hospitalisation or prolongation of existing hospital admission, threatening life, resulting in significant incapacity or disability, or otherwise considered important by the investigator.

TABLE 86 Other related adverse effects in years 1 and 2: uterine/vault cohort (CC3)

Adverse effect	Uterine			Vault		
Number of women in first year	*N* = 69			*N* = 146		
Intraoperative						
Injury to organs	0.0%	0	69	1.4%	2	146
Excess blood loss	0.0%	0	69	0.0%	0	146
Blood transfusion	1.4%	1	69	0.0%	0	146
Anaesthetic complications	0.0%	0	69	0.0%	0	146
Postoperative						
Thrombosis	0.0%	0	69	0.0%	0	146
Infection	0.0%	0	69	1.4%	2	146
Pain	0.0%	0	69	0.7%	1	146
Urinary retention	0.0%	0	69	0.0%	0	146
Bowel obstruction	0.0%	0	69	0.0%	0	146
Constipation	0.0%	0	69	0.0%	0	146
Excess blood loss	0.0%	0	69	0.0%	0	146
Vaginal adhesions	0.0%	0	69	0.0%	0	146
Haematoma	0.0%	0	69	0.0%	0	146
Skin tags	0.0%	0	69	0.0%	0	146
Granulation tissue	0.0%	0	69	0.0%	0	146
Urinary tract symptoms	0.0%	0	69	0.0%	0	146

continued

TABLE 86 Other related adverse effects in years 1 and 2: uterine/vault cohort (CC3) (*continued*)

Adverse effect	Uterine			Vault		
Death	0.0%	0	69	0.0%	0	146
Number of women with any complication in first year	*1.4%*	*1*	*69*	*2.7%*	*4*	*146*
Number of women in second year	*N* = 69			*N* = 146		
Thrombosis	0.0%	0	69	0.0%	0	146
Infection	0.0%	0	69	0.7%	1	146
Pain	0.0%	0	69	0.0%	0	146
Urinary retention	0.0%	0	69	0.0%	0	146
Bowel obstruction	0.0%	0	69	0.0%	0	146
Constipation	0.0%	0	69	0.0%	0	146
Excess blood loss	0.0%	0	69	0.0%	0	146
Vaginal adhesions	0.0%	0	69	0.0%	0	146
Haematoma	0.0%	0	69	0.0%	0	146
Skin tags	0.0%	0	69	0.0%	0	146
Granulation tissue	0.0%	0	69	0.0%	0	146
Urinary tract symptoms	0.0%	0	69	0.0%	0	146
Death	0.0%	0	69	0.0%	0	146
Number of women with any other complication in second year	*0.0%*	*0*	*69*	*0.7%*	*1*	*146*

Dichotomous variables are presented as '% *n N*'.

TABLE 87 Prolapse symptoms at 6 months, 1 year and 2 years: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women at 6 months	*N* = 54			*N* = 121		
POP-SS at 6 months	*4.3*	*(4.7)*	*53*	*5.8*	*(6.2)*	*120*
Number of women symptomatic	81.1%	43	53	82.5%	99	120
Prolapse-related QoL score	2.4	(3.1)	50	2.8	(3.4)	119
Number of women at 1 year	*N* = 57			*N* = 116		
POP-SS (overall score at 1 year)	5.2	(5.5)	55	5.5	(5.8)	115
Number of women symptomatic	83.6%	46	55	80.0%	92	115
Prolapse-related QoL score	2.4	(3.2)	53	2.5	(3.3)	113
Number of women at 2 years	*N* = 48			*N* = 104		
POP-SS (overall score at 2 years)	5.3	(5.9)	47	5.6	(5.7)	104
Number of women symptomatic	80.9%	38	47	79.8%	83	104
Prolapse-related QoL score	1.9	(3.0)	45	2.3	(2.9)	104

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Prolapse

POP-SS: range 0–28, where 0 = no symptoms and 28 = all seven symptoms all of the time; primary clinical outcome. *Prolapse-related QoL score*: 'Overall, how much do prolapse symptoms interfere with everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); primary quality-of-life outcome. *Symptomatic prolapse*: at least one prolapse symptom (POP-SS > 0).

TABLE 88 Individual prolapse symptoms at 6 months, 1 year and 2 years: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women at 6 months	*N* = 54			*N* = 121		
SCD any	24.5%	13	53	30.0%	36	120
SCD freq.	7.5%	4	53	11.7%	14	120
Pain any	20.8%	11	53	25.0%	30	120
Pain freq.	5.7%	3	53	8.3%	10	120
Abdo any	34.0%	18	53	37.5%	45	120
Abdo freq.	0.0%	0	53	7.5%	9	120
Back any	35.8%	19	53	36.7%	44	120
Back freq.	3.8%	2	53	7.5%	9	120
Strain blad. any	34.0%	18	53	30.8%	37	120
Strain blad. freq.	5.7%	3	53	10.0%	12	120
Blad. not empty any	49.1%	26	53	58.3%	70	120
Blad. not empty freq.	7.5%	4	53	19.2%	23	120
Bowel not empty any	50.9%	27	53	70.8%	85	120
Bowel not empty freq.	7.5%	4	53	19.2%	23	120
Actions necessitated by prolapse symptoms						
Fingers to ease discomfort	N/A	N/A	N/A	N/A	N/A	N/A
Extra hygiene measures	N/A	N/A	N/A	N/A	N/A	N/A
Fingers to help empty bladder	N/A	N/A	N/A	N/A	N/A	N/A
Fingers to help empty bowel	N/A	N/A	N/A	N/A	N/A	N/A
Digital evacuation of bowel	N/A	N/A	N/A	N/A	N/A	N/A
Number of women at 1 year	*N* = 57			*N* = 116		
POP-SS (overall score at 1 year)	5.2	(5.5)	55	5.5	(5.8)	115
SCD any	29.1%	16	55	32.2%	37	115
SCD freq.	12.7%	7	55	13.9%	16	115
Pain any	30.9%	17	55	26.1%	30	115
Pain freq.	3.6%	2	55	7.0%	8	115
Abdo any	30.9%	17	55	33.0%	38	115
Abdo freq.	9.1%	5	55	7.0%	8	115
Back any	36.4%	20	55	39.1%	45	115
Back frequent	7.3%	4	55	9.6%	11	115
Strain blad. any	29.1%	16	55	32.2%	37	115
Strain blad. freq.	5.5%	3	55	7.0%	8	115
Blad. not empty any	49.1%	27	55	56.5%	65	115
Blad. not empty freq.	12.7%	7	55	13.0%	15	115
Bowel not empty any	60.0%	33	55	66.1%	76	115
Bowel not empty freq.	12.7%	7	55	13.0%	15	115

continued

TABLE 88 Individual prolapse symptoms at 6 months, 1 year and 2 years: uterine/vault cohort (CC3) (*continued*)

Symptom	Uterine			Vault		
Actions necessitated by prolapse symptoms						
Fingers to ease discomfort	2.4%	1	42	0.0%	0	110
Extra hygiene measures	7.1%	3	42	8.4%	9	107
Fingers to help empty bladder	0.0%	0	46	0.9%	1	109
Fingers to help empty bowel	0.0%	0	44	1.9%	2	108
Digital evacuation of bowel	4.3%	2	46	4.6%	5	109
Number of women at 2 years	*N* = 48			*N* = 104		
SCD any	38.3%	18	47	36.5%	38	104
SCD freq.	12.8%	6	47	8.7%	9	104
Pain any	21.3%	10	47	23.1%	24	104
Pain freq.	2.1%	1	47	2.9%	3	104
Abdo any	27.7%	13	47	34.6%	36	104
Abdo freq.	4.3%	2	47	5.8%	6	104
Back any	36.2%	17	47	43.3%	45	104
Back frequent	10.6%	5	47	10.6%	11	104
Strain blad. any	38.3%	18	47	38.5%	40	104
Strain blad. freq.	12.8%	6	47	9.6%	10	104
Blad. not empty any	57.4%	27	47	55.8%	58	104
Blad. not empty freq.	17.0%	8	47	13.5%	14	104
Bowel not empty any	61.7%	29	47	69.2%	72	104
Bowel not empty freq.	17.0%	8	47	13.5%	14	104
Actions necessitated by prolapse symptoms						
Fingers to ease discomfort	0.0%	0	47	2.0%	2	101
Extra hygiene measures	10.6%	5	47	6.9%	7	101
Fingers to help empty bladder	0.0%	0	48	2.0%	2	102
Fingers to help empty bowel	2.1%	1	48	2.0%	2	102
Digital evacuation of bowel	2.1%	1	48	2.9%	3	102

N/A, not applicable.
Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Individual prolapse symptoms
Abdo. any: 'A heaviness or dragging feeling in your lower abdomen (tummy)?' (any = occasionally or more); *Abdo. freq.*: frequent = most or all of the time; *Back any*: 'A heaviness or dragging feeling in your lower back?' (any = occasionally or more); *Back freq.*: frequent = most or all of the time; *Blad. not empty any*: 'A feeling that your bladder has not emptied completely?' (any = occasionally or more); *Blad. not empty freq.*; frequent = most or all of the time; *Bowel not empty any*: 'A feeling that your bowel has not emptied completely?' (any = occasionally or more); *Bowel not empty freq.*: frequent = most or all of the time; *Pain any*: 'An uncomfortable feeling or pain in your vagina which is worse when standing?' (any = occasionally or more); *Pain freq.*: frequent = most or all of the time; *SCD any*: 'A feeling of something coming down from or in your vagina?' (any = occasionally or more); *SCD freq.*: frequent = most or all of the time; *Strain blad.* any: 'A need to strain (push) to empty your bladder?' (any = occasionally or more); *Strain blad. freq.*: frequent = most or all of the time.
Actions necessitated by prolapse symptoms
Digital evacuation of bowel: Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel? (most or all of the time). *Extra hygiene measures*: Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems? (most or all of the time). *Fingers to ease discomfort*: Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain? (most or all of the time). *Fingers to help empty bladder*: Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)? (most or all of the time). *Fingers to help empty bowel*: Do you have to insert a finger into your vagina to help empty your bowels? (most or all of the time).

TABLE 89 EuroQol-5 Dimensions (3-level version) at 1 year: uterine/vault cohort (CC3)

EQ-5D-3L	Uterine			Vault		
Number of women at 6 months	*N* = 54			*N* = 121		
Score	0.83	(0.22)	54	0.79	(0.27)	115
Number of women at 1 year	*N* = 57			*N* = 116		
Score	0.83	(0.26)	57	0.78	(0.27)	112
Number of women at 2 years	*N* = 48			*N* = 104		
Score	0.79	(0.28)	48	0.80	(0.31)	104

Continuous variables are presented as 'mean (SD) *N*'.

TABLE 90 Urinary symptoms at 1 year and 2 years: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women at 1 year	*N = 46*			*N = 112*		
Any incontinence	65.2%	30	46	68.5%	76	111
ICIQ-UI-SF score	4.7	(4.4)	45	5.0	(5.1)	108
Severe incontinence	6.7%	3	45	8.3%	9	108
Incontinence-related QoL score	2.1	(2.8)	45	2.0	(2.7)	106
Stress UI	17.9%	7	39	18.3%	17	93
Urgency UI	0.0%	0	46	0.9%	1	109
Overactive bladder	2.2%	1	46	0.9%	1	106
ICIQ-FLUTS filling score	3.5	(2.4)	46	4.2	(2.3)	106
ICIQ-FLUTS voiding score	1.5	(1.8)	46	1.7	(2.4)	108
ICIQ-FLUTS incontinence score	4.6	(3.0)	38	4.8	(4.0)	92
Number of women at 2 years	*N* = 48			*N* = 104		
Any incontinence	64.6%	31	48	65.4%	68	104
ICIQ-UI-SF score	4.7	(4.8)	46	4.5	(5.0)	103
Severe incontinence	8.7%	4	46	7.8%	8	103
Incontinence-related QoL score	1.9	(2.6)	46	1.8	(2.7)	98
Stress UI	17.1%	7	41	17.2%	15	87
Urgency UI	6.4%	3	47	2.9%	3	102
Overactive bladder	4.3%	2	46	2.0%	2	102
ICIQ-FLUTS filling score	4.0	(3.0)	46	4.1	(2.5)	102
ICIQ-FLUTS voiding score	1.7	(2.5)	48	1.7	(2.2)	102
ICIQ-FLUTS incontinence score	4.7	(3.5)	39	4.9	(4.3)	87

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Urinary symptoms

Any incontinence: Defined as 'How often do you leak urine?' (any frequency) and/or 'How much urine do you usually leak?' (whether you wear protection or not) (any amount); *Incontinence-related quality-of-life score*: 'Overall, how much does leaking urine interfere with your everyday life?' – using a VAS, score range from 0 (not at all) to 10 (a great deal); *International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score*: sum of responses to above three questions – range 0 (no incontinence symptoms) to 21 (leaking all the time, a large amount and affecting quality of life = 10); *Overactive bladder*, nocturia twice or more, and urinary urgency 'most or all of the time' and urinary frequency nine or more times per day; *Severe urinary incontinence*: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form score of 13–21; *Stress urinary incontinence*, 'Does urine leak when you are physically active, exert yourself, cough or sneeze?' (most or all of the time); *Urgency urinary incontinence*, 'Does urine leak before you can get to the toilet?' (most or all of the time).

The improvement at 1 year was maintained at 2 years, with respect to all the urinary outcomes and bladder-related QoL outcomes measured (*Table 90*).

Bowel symptoms

Detailed information on bowel symptoms was obtained at baseline, 1 year and 2 years (see *Tables 81* and *91*). Frequency of bowel movements, constipation, bowel urgency and FI were common and largely unchanged from baseline to after prolapse surgery in the uterine group at both 1 year and 2 years (*Table 91*).

Vaginal and sexual symptoms

Detailed information on vaginal and sexual symptoms was obtained at baseline, 1 year and 2 years (see *Tables 82* and *92*). Both the mean vaginal symptom score and the QoL score decreased (improved) after prolapse surgery, and this was maintained at 2 years (*Table 92*). More women were sexually active after surgery, and many fewer cited prolapse symptoms as a reason for not having a sex life (reduced from 36.1% to 12.0%). This was reflected in a more than halving of the ICI Sexual Matters score, and a reduction (improvement) to one-third of baseline levels in the sex life QoL score (see *Tables 82* and *92*). These improvements were maintained at 2 years.

Further treatment required for failure or adverse effects at 6 months, 1 year and 2 years

When women reported, at 6 months or later, that they had been readmitted to hospital, we verified the information by enquiry from site staff when necessary and post-coded the corrected information. A hospital readmission was automatically counted as a SAE if it was related to the initial prolapse surgery. Repeat surgery for recurrence of prolapse (failure if same compartment, de novo if in the opposite compartment), or for continence surgery, was differentiated from readmission for related complications such as bleeding, infection and surgery for mesh removal.

The overall rate of readmission was low (two women in the uterine group in the first 6 months; *Table 93*). Admissions in the first 6 months were related to adverse effects (pain). After that time, one woman had further surgery for prolapse in a different compartment, and one in the second year (see *Table 93*). No women required surgery for mesh removal at any time point.

Few women required other treatment – such as pessaries or physiotherapy – for symptoms.

Satisfaction with treatment at 1 year and 2 years

Although most women were better than before surgery by 1 year, around 10% (four women) were worse, with similar findings at 2 years (*Table 94*). This was reflected in the satisfaction rates and in the proportion of women who would recommend surgery to a friend.

Vault prolapse: women requiring a prolapse repair for vault descent alone

Women's characteristics at baseline

The mean age of women presenting with a vault prolapse alone was 62.5 years (see *Table 77*). This is older than the women who were having primary or uterine-only surgery in PROSPECT (see *Table 5*). However, the groups were generally all similar on other characteristics, such as parity, BMI and delivery mode history.

About one-third of the women with a vault prolapse had seen a physiotherapist, and about 1 in 10 were using a pessary for prolapse symptoms (see *Table 77*). One in five women had seen a physiotherapist for urine symptoms and around 1 in 10 had used drugs for urinary problems.

TABLE 91 Bowel symptoms at 1 year and 2 years: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women at 1 year	***N* = 46**			***N* = 112**		
Bowel frequency						
≥ 4 times a day	2.2%	1	46	0.9%	1	110
1–3 times a day	30.4%	14	46	30.0%	33	110
About once a day	43.5%	20	46	48.2%	53	110
Once every 2 or 3 days	21.7%	10	46	16.4%	18	110
Weekly or less	2.2%	1	46	4.5%	5	110
Constipation	21.7%	10	46	17.6%	19	108
Bowel urgency	2.2%	1	46	10.8%	12	111
FI (any)	23.9%	11	46	36.0%	40	111
Passive FI	100.0%	11	11	70.0%	28	40
Active FI	0.0%	0	11	30.0%	12	40
Severe FI	6.5%	3	46	13.5%	15	111
Bowel symptoms QoL score	1.8	(3.1)	46	2.3	(2.9)	110
Number of women at 2 years	***N* = 48**			***N* = 104**		
Bowel frequency						
≥ 4 times a day	0.0%	0	47	3.9%	4	103
1–3 times a day	25.5%	12	47	26.2%	27	103
About once a day	55.3%	26	47	47.6%	49	103
Once every 2 or 3 days	17.0%	8	47	19.4%	20	103
Weekly or less	2.1%	1	47	2.9%	3	103
Constipation	10.6%	5	47	19.2%	20	104
Bowel urgency	6.3%	3	48	3.9%	4	103
FI (any)	29.2%	14	48	37.9%	39	103
Passive FI	85.7%	12	14	87.2%	34	39
Active FI	14.3%	2	14	10.3%	4	39
Severe FI	10.4%	5	48	10.7%	11	103
Bowel symptoms QoL score	2.2	(3.2)	46	2.3	(2.9)	101

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Bowel symptoms

Active faecal incontinence: Any faecal incontinence when bowel urgency 'most or all of the time' is also reported; *Bowel symptoms QoL score*: 'Overall, how much do bowel symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); this could be due to any one or a combination of the above bowel symptoms. *Bowel urgency*: 'Do you have to rush to the toilet when you need to open (move) your bowels?' (most or all of the time); *Constipation (ROME criteria, adapted)*: any two of stool passing once a week or less, straining most or all of the time, hard stools, bowel not feeling empty most or all of the time, manual manoeuvre to empty bowel most or all of the time. *Faecal incontinence (any/severe)*: faecal incontinence of solid or liquid stool – 'Do stools (faeces, motion) leak at inappropriate time or place, or before you can get to the toilet?' (any = occasionally or more often; severe = sometimes, most or all of the time); *Passive faecal incontinence*: any faecal incontinence not accompanied by bowel urgency 'most or all of the time'.

TABLE 92 Vaginal and sexual symptoms at 1 year: uterine/vault cohort (CC3)

Symptom	Uterine			Vault		
Number of women at 1 year	*N* = 46			*N* = 112		
Vaginal						
ICIQ-VS score	8.2	(10.5)	41	7.2	(7.8)	97
Vaginal symptoms QoL score	2.0	(3.2)	43	1.8	(2.7)	105
Vagina too tight	2.3%	1	43	1.0%	1	104
Sexual						
Sex life at present	46.8%	22	47	36.9%	41	111
Reason for no sex life						
No partner	48.0%	12	25	40.0%	28	70
Vaginal symptoms	4.0%	1	25	4.3%	3	70
Prolapse symptoms	12.0%	3	25	7.1%	5	70
Other reason	28.0%	7	25	42.9%	30	70
Reason not given	8.0%	2	25	5.7%	4	70
Dyspareunia	8.3%	2	24	4.7%	2	43
ICI Sexual Matters score	11.0	(14.1)	24	10.8	(12.5)	42
Sex life QoL score	3.2	(3.7)	25	2.6	(3.3)	43
Number of women at 2 years	*N* = 48			*N* = 104		
Vaginal						
ICIQ-VS score	7.8	(8.2)	46	7.9	(8.6)	96
Vaginal symptoms QoL score	1.7	(2.6)	46	1.8	(2.8)	98
Vagina too tight	2.1%	1	48	2.0%	2	98
Sexual						
Sex life at present	47.9%	23	48	43.4%	43	99
Reason for no sex life						
No partner	52.0%	13	25	30.4%	17	56
Vaginal symptoms	0.0%	0	25	5.4%	3	56
Prolapse symptoms	8.0%	2	25	5.4%	3	56
Other reason	20.0%	5	25	44.6%	25	56
Reason not given	20.0%	5	25	14.3%	8	56
Dyspareunia	8.3%	2	24	2.3%	1	44
ICI Sexual Matters score	13.3	(13.9)	23	9.5	(11.4)	43
Sex life QoL score	2.8	(3.2)	25	2.4	(3.2)	46

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.

Vaginal and sexual symptoms

Dyspareunia (any, severe): pain during sexual intercourse (any = a little or somewhat; severe = a lot); *International Consultation on Incontinence vaginal symptoms score*: combination of responses to vaginal symptom questions; *Sex life quality of life*: 'Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal); *Vagina too tight*: 'Do you feel that your vagina is too tight?' (most or all of the time); *Vaginal symptoms QoL score*: 'Overall, how much do your vaginal symptoms interfere with your everyday life?' – measured using a VAS, score range from 0 (not at all) to 10 (a great deal).

TABLE 93 Further treatment required at 6 months, 1 year and 2 years: uterine/vault cohort (CC3)

Further treatment	Uterine			Vault		
Number of women at 6 months	***N* = 54**			***N* = 121**		
Readmitted (0–6 months)[a]	3.7%	2	54	1.7%	2	121
Number of women at 1 year	***N* = 57**			***N* = 116**		
Readmitted (6–12 months)[b]	0.0%	0	57	0.9%	1	116
New prolapse surgery	1.8%	1	57	4.3%	5	116
Same compartment	0.0%	0	57	1.7%	2	116
Different compartment	1.8%	1	57	2.6%	3	116
Waiting for prolapse surgery	0.0%	0	57	2.6%	3	116
Continence surgery	0.0%	0	57	0.0%	0	116
Waiting for continence surgery	0.0%	0	57	0.9%	1	116
Stitches removed since operation	0.0%	0	56	1.8%	2	114
Mesh complication	0.0%	0	57	0.0%	0	116
Treatment for urinary problems						
Pads	28.6%	16	56	38.6%	44	114
Permanent catheter	1.8%	1	56	0.9%	1	107
Intermittent catheter	3.6%	2	56	1.8%	2	109
Drugs for UI	3.5%	2	57	10.3%	12	116
Treatment for prolapse						
Medicines for prolapse	12.5%	7	56	20.4%	23	113
Oestrogens	17.5%	10	57	16.4%	19	116
Ring pessary	1.8%	1	57	2.6%	3	116
Shelf pessary	0.0%	0	57	0.0%	0	116
Physiotherapy	12.5%	7	56	9.1%	10	110
GP for prolapse	17.5%	10	57	21.3%	23	108
Practice nurse for prolapse	8.9%	5	56	2.7%	3	110
GOPD to see gynaecologist	41.8%	23	55	45.5%	50	110
Number of women at 2 years	***N* = 48**			***N* = 104**		
Readmitted (12–24 months)[c]	2.1%	1	48	0.0%	0	104
New prolapse surgery	2.1%	1	48	4.8%	5	104
Same compartment	0.0%	0	48	1.0%	1	104
Different compartment	2.1%	1	48	3.8%	4	104
Waiting for prolapse surgery	0.0%	0	48	0.0%	0	104
Continence surgery	0.0%	0	48	3.8%	4	104
Waiting for continence surgery	0.0%	0	48	0.0%	0	104
Stitches removed since operation	0.0%	0	46	1.0%	1	100
Mesh complication	0.0%	0	48	0.0%	0	104
Surgical removal in theatre	0.0%	0	48	0.0%	0	104
Conservative/GOPD procedure	0.0%	0	48	0.0%	0	104

continued

TABLE 93 Further treatment required at 6 months, 1 year and 2 years: uterine/vault cohort (CC3) (*continued*)

Further treatment	Uterine			Vault		
Treatment for urinary problems at 2 years						
Pads	31.3%	15	48	32.4%	33	102
Permanent catheter	0.0%	0	48	1.0%	1	101
Intermittent catheter	0.0%	0	47	0.0%	0	102
Drugs for UI	8.3%	4	48	10.6%	11	104
Treatment for prolapse in year 2						
Medicines for prolapse	8.3%	4	48	11.8%	12	102
Oestrogens	8.3%	4	48	16.3%	17	104
Ring pessary	4.2%	2	48	1.9%	2	104
Shelf pessary	2.1%	1	48	1.9%	2	104
Physiotherapy	10.9%	5	46	6.7%	7	104
GP for prolapse	21.3%	10	47	11.7%	12	103
Practice nurse for prolapse	6.4%	3	47	1.0%	1	102
GOPD to see gynaecologist	21.3%	10	47	13.6%	14	103

GOPD, Gynaecology Outpatients Department.
a Reasons for readmission (0–6 months): infection (1), other (3).
b Reasons for readmission (6–12 months): infection (1).
c Reasons for readmission (12–24 months): constipation (1).
Dichotomous variables are presented as '% *n* *N*'.

TABLE 94 Participant recovery and satisfaction: uterine/vault cohort (CC3)

Recovery/satisfaction	Uterine			Vault		
Number of women at 1 year	***N* = 46**			***N* = 112**		
Time to recovery (months)	2.8	(1.5)	40	3.4	(2.2)	101
Comparison of prolapse with before surgery						
Very much better	65.9%	27	41	64.7%	66	102
Much better	19.5%	8	41	18.6%	19	102
A little better	4.9%	2	41	4.9%	5	102
No change	0.0%	0	41	3.9%	4	102
A little worse	4.9%	2	41	2.9%	3	102
Much worse	2.4%	1	41	2.0%	2	102
Very much worse	2.4%	1	41	2.9%	3	102
Satisfaction with surgery						
Completely satisfied	63.4%	26	41	57.5%	61	106
Fairly satisfied	19.5%	8	41	26.4%	28	106
Fairly dissatisfied	4.9%	2	41	6.6%	7	106
Very dissatisfied	9.8%	4	41	6.6%	7	106
Not sure	2.4%	1	41	2.8%	3	106

TABLE 94 Participant recovery and satisfaction: uterine/vault cohort (CC3) (*continued*)

Recovery/satisfaction	Uterine			Vault		
Recommend to a friend	87.5%	35	40	93.3%	97	104
Number of women at 2 years	***N* = 48**			***N* = 104**		
Comparison of prolapse with before surgery						
Very much better	55.3%	26	47	59.2%	61	103
Much better	14.9%	7	47	24.3%	25	103
A little better	12.8%	6	47	6.8%	7	103
No change	6.4%	3	47	3.9%	4	103
A little worse	4.3%	2	47	2.9%	3	103
Much worse	0.0%	0	47	2.9%	3	103
Very much worse	6.4%	3	47	0.0%	0	103
Satisfaction with surgery						
Completely satisfied	56.3%	27	48	58.3%	60	103
Fairly satisfied	16.7%	8	48	27.2%	28	103
Fairly dissatisfied	8.3%	4	48	4.9%	5	103
Very dissatisfied	14.6%	7	48	8.7%	9	103
Not sure	4.2%	2	48	1.0%	1	103
Recommend to a friend	82.6%	38	46	90.0%	90	100

Continuous variables are presented as 'mean (SD) *N*'; dichotomous variables are presented as '% *n N*'.
Satisfaction with surgery
How is prolapse compared with before surgery? Very much better = cured [1]; much or a little better (or very much better) = improved or cured [< 4]; no change or worse = failed [> 3]. *Satisfied with results of operation*? Completely satisfied = cured [1]; fairly satisfied = improved or cured [1 or 2]; fairly or very dissatisfied = failed [3 or 4]; not sure = separate category [5].

Preoperative prolapse measurements

The leading edge of the upper compartment (point C on the POP-Q) was, on average, just inside the hymen (–0.4 cm for vault prolapse; see *Table 78*). The majority of women had stage 3 or 4 prolapse, unlike those having only an anterior or posterior repair, for whom the most common preoperative stage was stage 2 (see *Table 7*). Using a more strict definition of prolapse (leading edge > 0 cm beyond the hymen), 84.3% of women had a prolapse beyond the hymen.

Prolapse symptoms at baseline

All women had at least one prolapse symptom on the Pelvic Organ Prolapse Symptom scale, the most common of which was 'a feeling of something coming down from or in (your) vagina' (see *Table 79*). Women who were having a vault prolapse repair had a higher prolapse symptom score (POP-SS of 15.3) and more bother from their prolapse, based on their prolapse-related QoL score (7.3) than women who were having anterior or posterior repair (see *Tables 15* and *50*) or uterine-only repair (see *Table 79*). The principal individual prolapse symptom was a feeling of 'something coming down'. They were also more likely to need to use preventative manoeuvres or extra hygiene measures to relieve their prolapse and other symptoms of pelvic floor dysfunction (see *Table 79*).

Urinary symptoms at baseline

Based on a variety of validated measures of assessing bladder function, women with vault prolapse were similar to the other groups of women who were having prolapse surgery on nearly every measure. In particular, UI was just as prevalent: three in four women with any incontinence, and one in four with severe symptoms (see *Table 80*).

Bowel symptoms at baseline

Similarly, women with vault prolapse were similar to those with other types of prolapse with respect to most aspects of bowel function (see *Table 81*). About one-quarter had constipation and almost one-third had FI. Passive FI was much more common than active (FI accompanied by bowel urgency).

Vaginal and sexual symptoms at baseline

About one-third of women were sexually active (see *Table 82*). For those who did have a partner, the most common reason for no sex life was their prolapse symptoms. Around 15% of the women had dyspareunia (pain with intercourse) but the numbers were small.

Planned surgery and surgery actually carried out

To be enrolled in CC3, women were clinically assessed as not needing an anterior or posterior repair. Only six women were thought to need continence surgery (see *Table 83*), despite > 20% having severe urine incontinence.

Surgery actually received

The women in this cohort were thought to have a vault prolapse, and nearly 90% did, in fact, have a vault repair (see *Table 83*).

Description of surgical characteristics and protocols

The majority of women with a vault prolapse received surgery from a consultant gynaecologist (78.3%; see *Table 84*); if carried out by a junior doctor, the surgeon was supervised in around 90% of cases. Most women had a general anaesthetic, received prophylactic antibiotics and, on average, were in theatre for approximately 2 hours. The mean length of stay was just under 2 days.

Outcomes for women who were having a vault prolapse repair

Serious and other related adverse effects in first and second years

The proportion of women who had at least one serious adverse effect in the first year (excluding mesh complications) was 2.7% in the vault group (four women; see *Table 85*). One woman had serious infection and pain in the second year. No women had any incidence of mesh exposure.

Prolapse symptoms and EuroQol-5 Dimensions

At 6 months, the women's report of their prolapse symptoms, using the POP-SS (maximum score 28), fell from 15.3 for the vault group to 5.8 (see *Table 87*). Similarly, each individual prolapse symptom also improved (see *Table 88*), as did the prolapse-related QoL scores (see *Table 87*).

At 1 year, this improvement was maintained (POP-SS of 5.5 for the vault group; see *Table 87*). The improvement from baseline was supported by data from individual prolapse symptoms (measured as occurring 'ever' or 'most or all of the time'); the proportion of women who had at least one prolapse symptom ('symptomatic'); QoL data, based on the interference of prolapse symptoms on everyday life (see *Table 87*); the generic QoL measure EQ-5D-3L (see *Table 89*); and the need to undertake extra hygiene measures or manoeuvres to assist pelvic floor functions. All of these measures demonstrated significant improvements from before surgery.

The improvement at 1 year was maintained at 2 years, with respect to all of the prolapse outcomes and QoL outcomes measured.

Urinary symptoms

Detailed information on urinary symptoms was obtained at baseline, 1 year and 2 years (see *Tables 80* and *90*). The number of women who had concomitant continence surgery was 5/146 in the vault group (see *Table 83*).

At 1 year in the vault group, the proportion of women who had any UI decreased from 73.7% to 68.5% and the proportion with severe UI more than halved (from 23.8% to 8.3%; see *Tables 80* and *90*). There were similar moderate improvements in all of the other measures of bladder function measured. The improvement at 1 year was maintained at 2 years, with respect to all of the urinary outcomes and bladder-related QoL outcomes measured (see *Table 90*).

Bowel symptoms

Detailed information on bowel symptoms was obtained at baseline, 1 year and 2 years (see *Tables 81* and *91*). Frequency of bowel movements, constipation, bowel urgency and FI were common, and largely unchanged from baseline to after prolapse surgery in the vault group at both 1 year and 2 years (see *Table 91*).

Vaginal and sexual symptoms

Detailed information on vaginal and sexual symptoms was obtained at baseline, 1 year and 2 years (see *Tables 82* and *92*). Both the mean vaginal symptom score and the QoL score decreased (improved) after vault prolapse surgery, and this was maintained at 2 years. More women were sexually active after surgery, and many fewer cited prolapse symptoms as a reason for not having a sex life (reduced from 46.7% to 5.4% in the second year; see *Tables 82* and *92*). This was reflected in a more than halving of the ICI Sexual Matters score and a reduction (improvement) to one-third of baseline levels in the sex life QoL score.

Further treatment required for failure or adverse effects at 6 months, 1 year and 2 years

When women reported, at 6 months or later, that they had been readmitted to hospital, we verified the information by enquiry from site staff when necessary and post-coded the corrected information. A hospital readmission was automatically counted as a SAE if it was related to the initial prolapse surgery. Repeat surgery for recurrence of prolapse (failure if same compartment, de novo if in the opposite compartment), or for continence surgery, was differentiated from readmission for related complications, such as bleeding, infection and surgery for mesh removal.

The overall rate of readmission was low (two women in the vault group in the first 6 months; *Table 93*). Admissions in the first 6 months were related to adverse effects (constipation and pain). After that time, five women had further surgery for prolapse (two in the same and three in a different compartment, and five in the second year; see *Table 93*). No women required surgery for mesh removal at any time point.

Few women required other treatment – such as pessaries or physiotherapy – for symptoms.

Satisfaction with treatment at 1 year and 2 years

Although most women were better than before surgery by 1 year, around 12% (12 women) were unchanged or worse, with similar findings at 2 years (see *Table 94*). This was reflected in the satisfaction rates, and in the proportion of women who would recommend surgery to a friend (90.0%).

Discussion

Summary of findings

This chapter has reported the findings for the cohort of women (CC3) who were not eligible for the randomisation arms of PROSPECT because they were not thought to need either an anterior or posterior repair. The women who were having vault prolapse were clearly a different population from those with uterine prolapse, based on epidemiological and clinical characteristics. They have therefore been described separately.

Chapter 9 Modelling

Little is known about the prevalence and effectiveness of different types of treatments for prolapse, except that they are prone to failure: around 30% of women undergo further operations. The mean time interval to the first secondary operation is about 12 years, and the time interval between subsequent procedures decreases with each successive repair.[4]

Gynaecologists have recognised for some time that both anatomical failure of supporting pelvic structures and recurrence of prolapse after surgery are common. It has also been recognised that surgery can be followed by a greater impairment of QoL than the original prolapse itself (e.g. new UI after surgery). In addition, repair of one type of prolapse may predispose the women to the development of a different type of prolapse (a new, or de novo, prolapse) in another compartment of the vagina due to alteration in the dynamic forces within the pelvis.[4]

This chapter focuses on presenting the methods and the results of a de novo economic model to guide decision-makers on the cost-effectiveness of alternative surgical procedures for primary prolapse repair.

Although the within-trial cost-effectiveness results are informative regarding short-run costs and QALYs for alternative treatments for the surgical management of primary prolapse repair, it is important to note that prolapse is a chronic condition and the effects of treatment on costs and outcomes may persist into the future. Therefore, we have developed a model to extrapolate the findings of the 2-year within-trial analysis to a longer-term period.

Modelling approach

A probabilistic Markov model was developed (Treeage Pro™ software 2014, TreeAge Software, Inc., Williamstown, MA, USA) to estimate expected values for costs and QALYs for different primary surgical prolapse repair strategies (standard repair, synthetic mesh and biological graft) over a base-case time horizon of 5 years. Results were obtained with a Monte Carlo (probabilistic or second-order) simulation of the developed Markov model with 1000 iterations. The model parameters were drawn from appropriate distributions attached to baseline data, relative effect sizes, costs and utilities. Baseline results were presented as mean costs and QALYs from the iterations, and the simulation was used to present uncertainty in modelled outcomes. Uncertainty is presented as incremental scatterplots on the cost-effectiveness plane and CEACs.

The model describes the treatment outcomes and follow-up of women who were having a primary prolapse repair. The perspective adopted is that of the UK NHS. Costs were based on 2013–14 UK pound sterling (£) values.

Model framework

The model was developed to extrapolate results of the Primary trial analysis (2-year follow-up) to a longer (5-year) time horizon. As prolapse is a chronic condition, with the potential for long-term failure and complications following surgery, a Markov state-transition decision-analytic model was used to represent these stochastic processes that evolve over time (in this case, monthly cycle lengths). The structure of a Markov model allows patients to move between defined mutually exclusive health states in a controlled manner over specified time periods. The pathways presented and transitions allowed within the model were developed in consultation with clinicians and trial collaborators.

The Markov model structure is outlined in *Figure 27*.

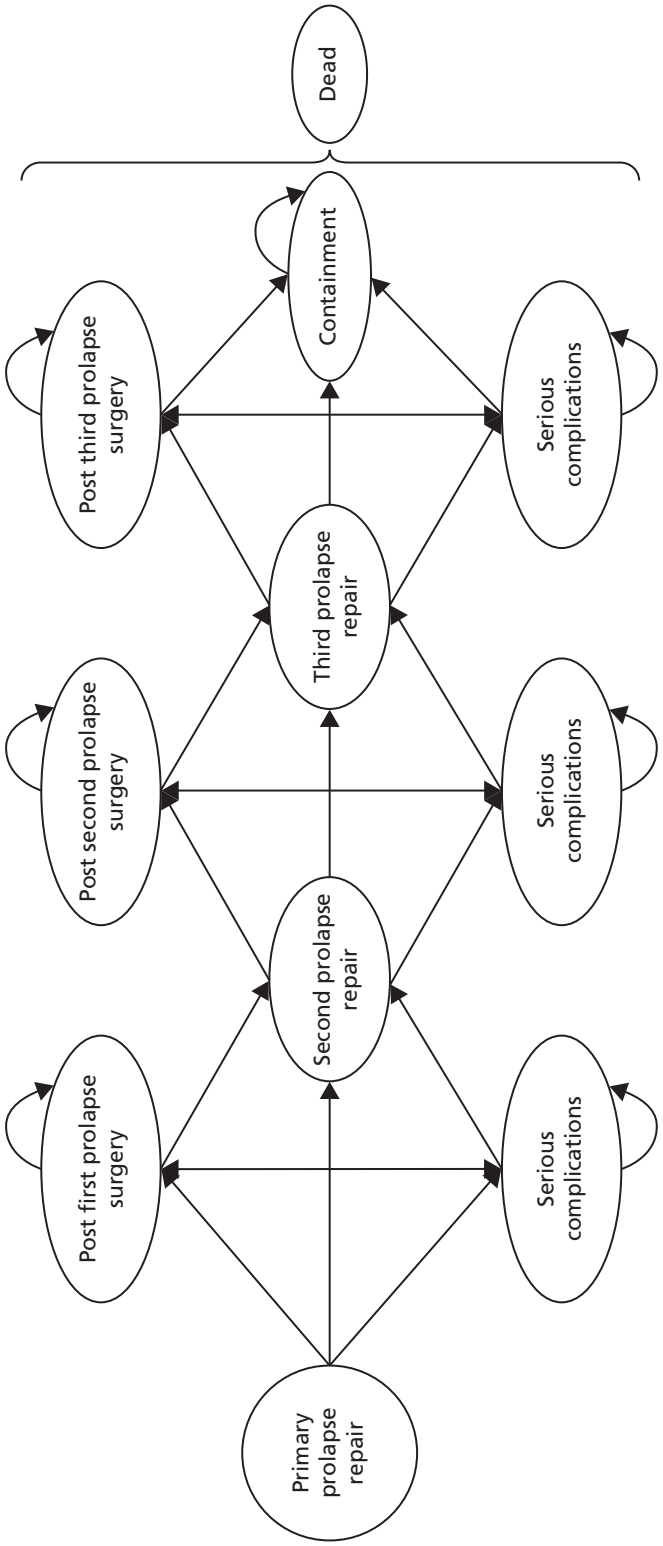


FIGURE 27 Markov model structure: primary prolapse repair.

All women enter the model in the 'primary prolapse repair' health state, for which they receive surgery. This initial 'primary prolapse repair' surgical state is set to the duration of three monthly cycles to reflect the likely time to recovery from prolapse surgery. After their initial surgical treatment, women then move into one of four mutually exclusive health states.

1. They may enter the 'post-prolapse surgery' health state (defined as women who are not experiencing serious complications or requiring repeat prolapse surgery). Within this health state, some women will still experience some prolapse-related symptoms or other (non-serious) complications* and may receive treatments for this, including physiotherapy or oestrogen treatments. Others will not require any further treatment in that cycle and are considered to be 'stable'. Women might stay in this state for the duration of the model (if they do not experience serious complications or require repeat prolapse surgery). At the end of each monthly cycle, they may transition from this state if they have serious complications, require further prolapse surgery or die.
2. Women may suffer serious complications at any point (as defined in the clinical classification of complications) following their surgery. If a woman experiences serious complications, she enters the 'serious complications' health state and receives treatment. Serious complications may be mesh or non-mesh related. Some will require surgery to address their complications. A woman who is experiencing serious complications might have these resolved during a single monthly cycle or might require to remain in the health state for a longer time period until the complications resolve.
3. Women might suffer a recurrence of their prolapse, which requires further repeat prolapse surgery at any time. For these women, surgery is deemed to have failed. For the purposes of this model, a failure is considered as a requirement for further prolapse surgery. Women who experience failures that are not requiring surgery remain in the post-prolapse surgery health state (see '1', above). Women who were having a failure requiring surgery enter the 'second surgery' health state, for which they go through a similar model process as those following their first repair. A failure requiring surgical repair is considered to be any repeat prolapse surgery, whether it occurs in the same or a different compartment.
4. There is a small chance that a woman may die from natural causes. The 'death' state considers that women may die from any causes at any point in time and this is assumed to be all-cause mortality.

[Note: *The complications have been classified in accordance with the trial reporting of adverse effects as serious mesh complications, serious non-mesh complications, other mesh complications and other non-mesh complications. 'Other' complications have been defined as those that were not categorised as serious adverse effects for trial reporting, but may still have had a significant impact on quality of life and use of health services. Complications were considered 'serious' if they met one or more of the following criteria: the complications (1) resulted in the patient's death, in which case they progressed straight to the death state in the model; (2) resulted in hospitalisation; (3) resulted in prolongation of an existing hospital stay; (4) lead to persistent or significant disability or incapacity; (5) were life-threatening; and (6) were considered medically significant by the trial investigator.]

Table 95 illustrates the treatment sequences for primary prolapse repair and any further repair surgery. The women receive a maximum of two further prolapse surgical repairs. Women who are still found to have prolapse failure after the third surgical procedure are assumed to proceed to containment management. This includes the use of pessaries, physiotherapy and regular outpatient consultation.

TABLE 95 Treatment sequence

First treatment	Second treatment	Third treatment
Standard repair	Second surgery	Third surgery
Synthetic mesh inlay		
Biological graft		

The follow-up treatments are assumed to be the same for all the women, as there is no evidence to inform the specific follow-up treatments. Clinical expert opinion (Professor Cathryn Glazener, University of Aberdeen, July 2015, personal communication) indicates that women may get any of the considered options as a secondary repair (e.g. standard, mesh inlay or mesh kit). Therefore, for the purposes of the economic analysis, all of the types of surgery are grouped together for the second and third prolapse repair as an aggregate of outcomes reported for the Secondary trial (see *Chapter 5*).

Survival analysis, based on time-to-event data, is used to guide the proportion of the modelled cohort progressing to repeat surgery health states and is outlined in more detail later in the chapter.

Women can continue moving through the states in the model for a maximum of 5 years (equivalent to 60 monthly cycles). A monthly cycle length has been chosen to reflect the time increments for which data regarding time of treatment failure and complications requiring surgery were available. This time horizon was selected as the study follows up patients for only 2 years and there are no long-term follow-up data. Costs and benefits that occur in the future were discounted following the standard practice, that is the recommended 3.5% for both costs and benefits (NICE 2013[38]).

Summary of the key assumptions made in the economic model

Details regarding the choice of data used to populate the model together with justifications for any assumptions made are outlined throughout the remainder of this section.

Assumptions related to the structure of the model

- The average age of women considered in the model is 59 years. This is the average age of the women who took part in the primary RCT. In the sensitivity analysis, different ages were considered.
- The cycle length of the model is 1 month. This cycle length was chosen to take in account the time to failure that was recorded in the trial.
- Cumulative costs and benefits are estimated for the 5-year period. In sensitivity analysis, the effect of a longer-term follow-up (10 years) was considered, although data to populate longer time to effect analysis are sparse and highly uncertain.
- Women who are in the 'post-prolapse repair' health state may be stable, but may also experience prolapse-related symptoms, and may also have prolapse failure (not requiring surgery). These are defined as women using containment products and they receive a utility decrement and additional cost within the 'post-prolapse surgery' health state. However, they do not require or receive surgery in that state but may do so at a point in the future.
- Women experiencing a repeat surgery are assumed to remain in the 'second prolapse repair' health state for a duration of 6 months. This is to allow for the time required to diagnose the failure, waiting list for treatment and a period of convalescence following surgery.
- Women experiencing serious complications may have their complications resolved within 1 month, or a proportion will remain with longer-term unresolved complications, assumed to be 25% resolved within 1 month, 50% within 3 months, 75% within 6 months and all resolved within 1 year.

Assumptions relating to the treatments offered

- The treatment strategies compared different initial treatments, namely standard midline repair, synthetic mesh and biological graft. Women requiring secondary repair surgery were assumed to receive the costs and outcomes associated with an aggregate of all of the secondary repairs (i.e. standard repair, mesh inlay or mesh kits). In reality, women may decide to receive specific secondary treatments that are deemed appropriate in conjunction with their clinicians.

- In the model, women were assumed to move into the containment failure management state (which is an absorbing state as they cannot leave it) after they had three surgeries. In reality, women whose symptoms recur may continue to seek surgical treatment until their symptoms are satisfactorily resolved. However, there are no data to populate this level of detail within the model, and, as such, the impact on cost-effectiveness is likely to be small, given the low proportion of women receiving three prolapse repairs within our modelled time horizon.
- Women are assumed to enter the containment arm of the model if they receive containment products that included medicines, oestrogens, pessaries and physiotherapy. Women may also receive these products without surgical repair, in which case they receive a utility decrement and additional cost within the 'post-prolapse surgery' state of the model (if they have not progressed through all three surgical repairs). This allows for the fact that women may get containment products on an ongoing basis, without surgical repair, or although they wait to see if symptoms clear up before requiring surgery.

Assumptions relating to data to populate the economic model

- Long-term estimates of failures and complication rates were based on the extrapolation of trial data from the three-way comparison (RCT1A).
- It was assumed that probabilities of failure and complications following a third repair surgery were equal to those following a second repair surgery.
- The costs of the second and third surgery were based on the aggregate cost of all three secondary treatment (standard midline repair, synthetic mesh and mesh introducer kits) surgeries from the trial data, as it was considered there was an equal chance that patients could receive any of the treatments.
- The model also took into account that some of the women did not have any further surgical treatments but may have had no surgical treatments, such as pessaries and other containment products as well as physiotherapy. Costs were attached to a proportion of the women in different cycles, as well as those in the containment state.

Estimation of model parameters

The model is parameterised using data from the three-way trial comparison (RCT1A) and relates only to women who were having a primary prolapse repair. When sufficient data were not available for individual model parameters from the trial, published and unpublished evidence in the field was consulted and, laterally, clinical expert opinion was used to populate any remaining parameters.

The methods used to assemble data followed recognised methodology, which varied according to the type of parameter, extent of uncertainty and role within the model. The modelling exercise complied with recent recommendations on good practice for modelling[63] and the results are presented in terms of incremental cost per QALY gained.

Mortality parameters

As women move through the model there is a chance that they may die. This chance is based on the annual rates of age-specific all-cause mortality for women (Office for National Statistics interim life tables[46]). As there were no intraoperative deaths reported during the PROSPECT trial in primary repair women, we have not added any additional surgical mortality to treatments. Furthermore, as there were relatively few deaths and no difference across arms regarding mortality over follow-up, no additional mortality risk that was specifically related to prolapse was applied.

Probability parameters

The main probabilities for the model are the probabilities of developing failures and complications. Probabilities reported in the tables to follow are adjusted, as appropriate, to reflect the model cycle length of 1 month using Treeage Pro's 'probtoprob' function.

Treatment failures

The probability of treatment failure is included within the model in two distinct ways. First of all there is a probability of failure, which may not require surgery and may be managed using conservative/containment techniques, as outlined above. Probabilities of conservatively managed failure are elicited directly from RCT1A of the trial for 1 year and 2 years, respectively. The longer run probability of failure requiring containment products is assumed to remain static at the 2-year probability over the remainder of the model time horizon. *Table 96* presents data for the probability of failure requiring conservative treatment management. Uncertainty was incorporated surrounding the estimates by sampling from a beta distribution, for which the alpha parameter is the number of events of interest (in this case the number of women with a conservatively managed failure) in the standard repair arm. The beta parameter is given as the total number of women in the standard repair arm minus the number of women with the event of interest.

The probability of failure, managed conservatively, following a secondary repair was assumed to be equal to that following a primary repair procedure, but was not incorporated as treatment-specific estimate within the model. The probability of having a conservative failure (not requiring surgery) beyond 2 years was assumed to remain constant for the remainder of the modelled time horizon.

Second, the more serious failures are defined as those that require further surgery (i.e. a secondary prolapse repair). There is conflicting evidence on the long-term failure (requiring surgery) rates for prolapse repairs, and hence significant uncertainty regarding the transition probabilities for the model. Transition probabilities to the health state of second and, subsequently, third prolapse surgery were estimated using survival analysis of time-to-event data over 2-year follow-up for the primary (RCT1A) and secondary (RCT2) trials, respectively. As outlined previously, women who were having a third failure were assumed to be treated using conservative management for the remainder of the model beyond having a third failure.

Extrapolation of the long-term reoperation rates for time to first failure (and time to second failure from the Secondary trial data) were presented using Kaplan–Meier survival curves, using a Weibull distribution. The formula used for the survival function is given as *Equation 2*. *Equation 3* presents the formula that was used to estimate transition probabilities for the baseline standard repair treatment:

$$S(t) = \exp(-\lambda t^{\gamma}) \tag{2}$$

$$tp = 1 - \{(\exp(-\lambda t^{\gamma})/\exp(-\lambda(t-1)^{\gamma})\}, \tag{3}$$

where:

- **S(t)** is the survival function representing the probability of success (i.e. not experiencing a prolapse failure).
- **tp** represents the formula for calculating transition probabilities to the failure health state for each monthly cycle in the model.
- **t** is the time (measured in terms of the number of cycles, for which each cycle is equivalent to 1 month).
- λ is the constant parameter from the regression model; this is the scale parameter that shows the probability that a woman's prolapse will recur in the next period, given the fact that she was successful in the current period.

TABLE 96 Baseline probabilities applied to conservative failure events

Variable	Time point (year)	Point estimate	Alpha	Beta	Distribution applied	Source
Conservative managed failure (primary repair)	1	0.0837	18	197	Beta	RCT1A trial data
	2	0.0576	11	180		

- γ is the shape parameter that describes the rate of change in the probability that a woman will have a recurrence of prolapse over time (i.e. that she will have failure). Shape parameters of > 1 indicate an increasing rate over time, whereas shape parameters of < 1 indicate a decreasing rate over time.

The above formula was adjusted by the appropriate hazard ratios to estimate transitions for the synthetic mesh and biological graft repair arms, respectively. Uncertainty is incorporated into the model by using the Cholesky decomposition of the covariance matrix estimated from the output of the Weibull regression models. A multinormal distribution was used to sample from the appropriate table containing Cholesky decomposition estimates multiplied by the coefficient of the log of the hazard ratios, lambda and gamma parameters. All statistical analyses of time-to-event data were estimated using Stata version 14 statistical analysis software. Using this process it was possible to estimate a hazard function using the values reported in *Table 97*.

Figure 28 shows the shape of the Kaplan–Meier curves that were fitted to the data reported in *Table 97*.

Time until the first major surgical procedure for prolapse failure was estimated using the survival time regression models with a Weibull distribution specified above. The hazard ratio was 1.075 (95% CI 0.495 to 2.335) for synthetic mesh compared with standard repair, and as 1.164 (95% CI 0.551 to 2.459) for biological graft compared with standard repair, based on adjustment for all minimisation covariates included in the regression model. Without adjustment, and examining only the hazard ratios, based on the observed data directly, unadjusted hazard ratios were 1.214 (95% CI 0.598 to 2.462) and 1.359 (95% CI 0.681 to 2.710) for synthetic mesh and biological graft repairs, respectively.

TABLE 97 Values used in the estimation of long-term failure after receiving prolapse treatment

Treatment	λ (lambda)	γ (gamma)	Hazard ratio: mean (95% CI)	
			Non-adjusted	Adjusted[a]
Standard midline	0.000615	1.408625		
Synthetic mesh	0.000764	1.408625	1.214 (0.598 to 2.462)	1.075 (0.495 to 2.335)
Biological graft	0.000835	1.408625	1.359 (0.681 to 2.710)	1.164 (0.551 to 2.459)

a Adjusted for minimisation variables as outlined in *Chapter 2*.

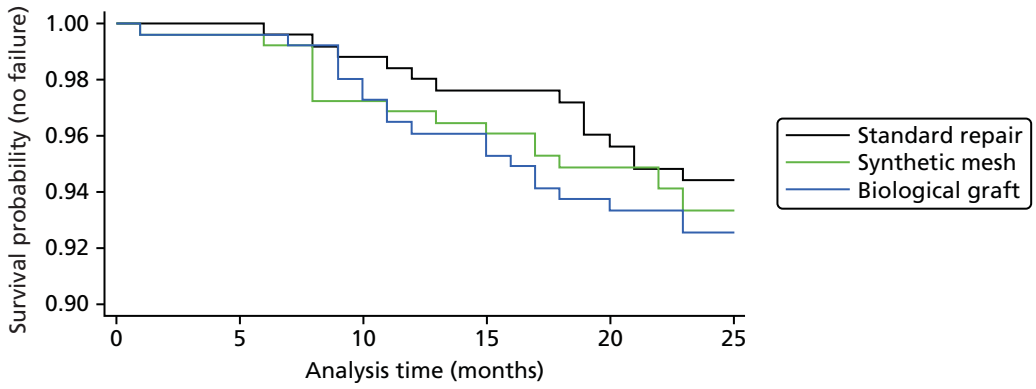


FIGURE 28 Kaplan–Meier survival estimates for surgery for prolapse failure.

Based on these data, there is no evidence of a difference between groups in terms of time to failure event at 2 years, with hazard ratios close to '1' indicating near equivalence between the groups. This estimate is generated using a model specifying a Weibull distribution. In order to select the appropriate model, we undertook a two-stage process. First, we tested and rejected ($p = 0.66$) the proportional hazards assumption using a Cox proportional hazards model. The next step was to select an appropriate distribution for the extrapolation model. A number of potentially appropriate distributions exist. Each was evaluated independently and likelihood ratio tests reported. None of the explored distributions performed particularly well, given the few data available. Likelihood ratio tests were conducted for log-logistic, Gompertz, exponential and Weibull distributions. In reality, any of these distributions could have been chosen. We selected a Weibull because of its wide use in economic evaluation literature and its flexible mathematical characteristics were deemed appropriate for use in this analysis. [We rejected the proportional hazards assumption for the Cox proportional hazards model ($p = 0.6598$). We then compared the following distributions on the basis of their likelihood ratio (chi-squared) and associated p-values: (A) log-logistic (likelihood ratio 0.81; $p = 0.67$); (B) Gompertz (likelihood ratio 0.77; $p = 0.68$); (C) exponential (likelihood ratio 0.76; $p = 0.68$); (D) Weibull (likelihood ratio 0.68; $p = 0.68$).]

Estimated CIs from both the adjusted and unadjusted regressions are wide, in part as a result of the relatively small number of failures requiring surgery across all three groups. Nonetheless, there is evidence that the prolapse failure rate increases over time, but at a declining rate, yet the proportional hazards model cannot be rejected.

Transition probabilities to third prolapse surgery, that is, long-term failure (requiring surgery) following a secondary repair surgery, are estimated using data from the Secondary trial analysis (see *Chapters 6* and *7*). Analysis was not treatment specific and, instead, incorporated failures for all women in the Secondary trial. Methods were similar to those estimating failure following a primary surgical repair. The associated Kaplan–Meier plot for all secondary surgery repairs together is presented in *Figure 29*.

The probability of further failure, following a third surgical repair, was assumed to be equivalent to the probability of failure following a secondary repair. At this point, it was assumed that women received only containment management and entered the absorbing, containment state, at which they remained for the duration of the model with a probability of all-cause mortality.

Complications

The probabilities of complications are divided into two distinct groups, namely mesh complications and non-mesh-related complications. These are further subdivided according to whether they were classified as SAEs within the trial or other adverse effects/complications. All of the complications included in the model were related to the prolapse repair preceding their occurrence. For example, complications following a primary repair were assumed to be related to the primary repair, complications following a secondary

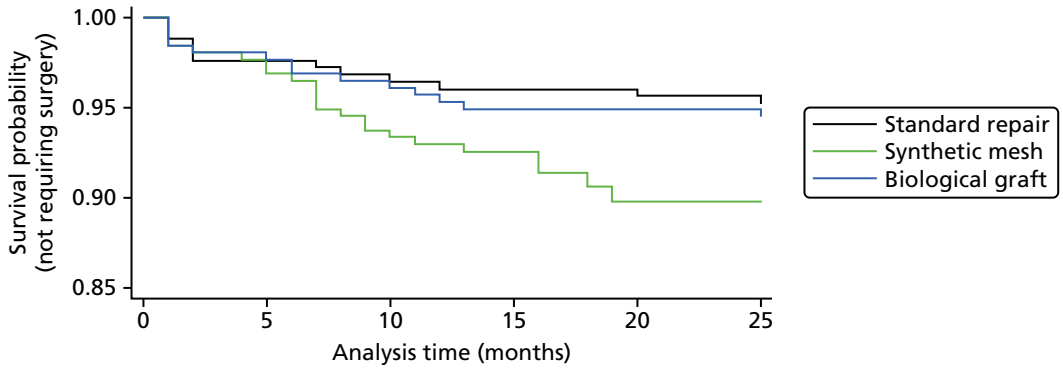


FIGURE 29 Kaplan–Meier survival estimates for surgery for prolapse failure (secondary). The Kaplan–Meier curve relates to all women who were having a secondary prolapse repair regardless of treatment strategy. Data are sourced from secondary repair trials (RCT2 and RCT3).

repair were assumed to be related to the secondary repair, and so on. Data are incorporated separately for 1- and 2-year outcomes to reflect the drop in complications over time. Baseline complications are determined according to the events observed within RCT1A (primary three-way trial comparison) for the standard repair arm of the trial.

Table 98 presents data for the probability of the various estimates of complications included in the model. Uncertainty surrounding the estimates was incorporated by sampling from a beta distribution, for which the alpha parameter is the number of events of interest (in this case, the number of women with a conservatively managed failure) in the standard repair arm. The beta parameter is given as the total number of women in the standard repair arm minus the number of women with the event of interest (i.e. a complication). It should be noted that these data are based on RCT1A only, and, as such, are not directly comparable with the complications data that were reported for trial 1 in *Chapter 4*.

TABLE 98 Baseline probabilities for complications events

Variable	Following surgery	Time point	Point estimate	Alpha	Beta	Distribution applied	Source
Serious mesh complications	Primary	1 year	0.004	1	251	Beta	RCT1A data
Serious non-mesh complications			0.063	15	237		
Other mesh complications			0.000	0.00001	251.99999		
Other non-mesh complications			0.063	17	235		
Serious mesh complications	Primary	2 years	0.004	1	251	Beta	RCT1A data
Serious non-mesh complications			0.012	4	248		
Other mesh complications			0.000	0.00001	251.99999		
Other non-mesh complications			0.024	8	244		
Serious mesh complications	Secondary	1 year	0.025	10	387	Beta	RCT2, CC2
Serious non-mesh complications			0.083	33	364		
Other mesh complications			0.020	3	150		
Other non-mesh complications			0.092	14	139		
Serious mesh complications	Secondary	2 years	0.007	1	152	Beta	RCT2, CC2
Serious non-mesh complications			0.020	3	150		RCT1A data
Other mesh complications			0.007	1	152		RCT2, CC2
Other non-mesh complications			0.033	5	148		

Probabilities for secondary complications are based on all Secondary trial women plus those in the CC. Treatment-specific estimates were not included for the Secondary trial.

Beyond the trial follow-up period, because of the low numbers of complications reported at 2-year time point in the trial, we assume that the probabilities of 'other' complications are '0' beyond 2 years. The probability of serious complications beyond 2 years is estimated using a time-to-event analysis to project rates of complications requiring surgery over the longer time horizon of the model.

Surgery for complications

The probability of complications beyond 2 years was restricted to only those women requiring surgery, as this is the most costly and serious of all complications, with the greatest impact on QoL. Owing to small numbers at 2 years, there was insufficient evidence to project differences and relative risks for each of the four categories of complications to the longer term. However, dates of surgery for women with complications (e.g. mesh removal surgery) were available and included in a time-to-event analysis. The methods and formulae used to generate model transition probabilities to the serious complications state for surgery are similar to those reported in the above section, *Treatment failures*. *Table 99* presents the parameters and hazard ratios used for the analysis of time to first surgery for serious complications.

Figure 30 presents the Kaplan–Meier curves describing the data that were used to project longer-run transition probabilities for complications requiring surgery, beyond the 2-year follow-up.

Analysis of time until the first surgical procedure for complications related to prolapse surgery estimated the hazard ratio as 2.558 (95% CI 1.123 to 5.825) for synthetic mesh compared with standard repair, and as 1.173 (95% CI 0.450 to 3.055) for biological graft compared with standard repair. Based on these data, surgery for complications occurs more often and earlier in the synthetic mesh group than in the standard repair group. This difference is driven by mesh complications in the synthetic mesh group. The estimation models for the hazard ratio are adjusted for baseline utility (QoL) and other minimisation variables,

TABLE 99 Values used in the estimation of long-term serious complications requiring surgery

			Hazard ratio: mean (95% CI)	
Treatment	λ (lambda)[a]	γ (gamma)[a]	Non-adjusted	Adjusted
Standard midline	0.00588	0.6588213		
Synthetic mesh	0.0129	0.6588213	2.196 (1.108 to 4.353)	2.558 (1.123 to 5.825)
Biological graft	0.00681	0.6588213	1.158 (0.536 to 2.504)	1.173 (0.450 to 3.055)

a Lambda and gamma parameters refer to unadjusted raw data model with Weibull-fitted distribution assumed.

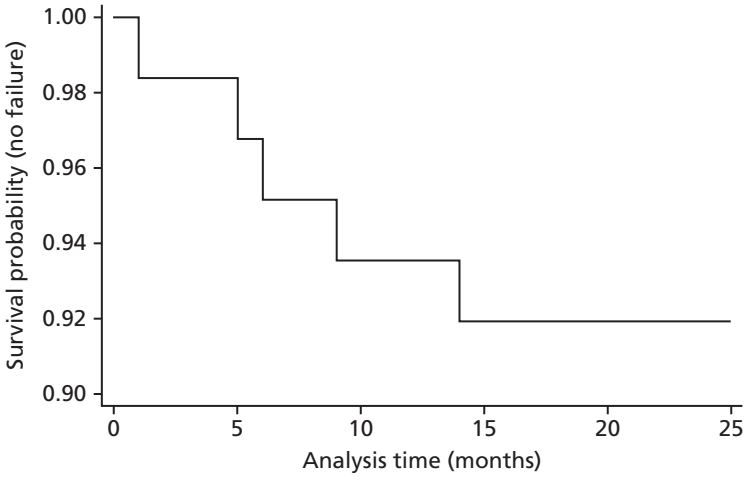


FIGURE 30 Kaplan–Meier survival estimates for surgery for serious complications.

as outlined in *Chapter 2*. Estimating the same hazard ratios, based on raw data only, without adjustment, the hazard ratios were 2.196 (95% CI 1.108 to 4.353) and 1.158 (95% CI 0.536 to 2.504) for synthetic mesh and biological graft repairs compared with standard repair, respectively.

There were no apparent differences in complications requiring surgery between the biological graft and the standard repair groups, although CIs were wide, in part due to the relatively small number of complications requiring surgery across these two groups.

Data from the estimates of time to event are used to estimate transition probabilities in the decision-analytic model. As with the analysis of time to surgery for prolapse failure, the analysis of surgery for complications is based on Weibull regression models to project data shown at 2 years in *Figure 30* over the longer-term time horizon required to populate the decision model. The decision to use a Weibull distribution followed a similar logic to that for the extrapolation of failure data. [Details of likelihood ratio tests for alternative distributional assumptions: we rejected the proportional hazards assumption for the Cox proportional hazards model ($p = 0.2934$). We then compared the following distributions on the basis of their likelihood ratio (chi-squared) and associated *p*-values: (A) log-logistic (likelihood ratio 6.48; *p*-value = 0.04); (C) log-normal (likelihood ratio 5.39; *p*-value = 0.07); (D) Gompertz (likelihood ratio 6.48; *p*-value = 0.04); (E) exponential (likelihood ratio 6.70; *p*-value = 0.04); and (F) Weibull (likelihood ratio 6.57; *p*-value = 0.04).] Following examination of the goodness of fit of the respective models (all of the assumed distributions performed equally well), we chose a Weibull because of its extensive use in economic evaluation literature and its flexible mathematical properties. Transition probabilities are calculated for monthly cycles of the model. A similar, but not treatment-specific, analysis was undertaken to project long-term complications for all of the women who were having surgery following a secondary repair. Data from this analysis are presented in *Appendix 6*. Owing to a lack of appropriate data to populate the model, we did not consider complications following a third prolapse procedure.

Relative risk parameters

For time-to-event parameters, hazard ratios were used to assign relative effect sizes to the time to experience a failure/surgery for complications. Uncertainty in these estimates was incorporated through the use of Cholesky decomposition matrices, as outlined in the *Probability parameters* section above. In relation to parameters based on proportions (conservative treatment for failure and non-surgical complications), absolute parameter values for synthetic mesh repair and biological graft repair were calculated by applying relative effect sizes (for synthetic mesh and biological graft vs. standard repair) to baseline probabilities. All of the relative effect sizes were incorporated into the model as point estimates of relative RRs with 95% CIs, estimated using the within-trial data as detailed in *Chapters 2* and *4*. Owing to a lack of data to inform longer-term extrapolation of each individual parameter beyond the trial follow-up, we have projected the probabilities of only complications requiring surgery or failures requiring surgery beyond 2 years. We rely on the time-to-event analyses described above to guide these model probabilities.

Furthermore, in instances for which baseline data may not have been available or zero events were observed in either the standard or comparison groups (e.g. serious mesh complications in the standard repair arm at 2 years were zero), raw data on probabilities in the comparator arms was used to populate the model in the place of relative risk estimates. When this is the case, it is clearly outlined in *Table 100* and the probability distributions used are outlined in *Table 101*. Relative risk data were not applied to probabilities following a secondary surgery, as it was not possible to know whether failure of a second repair was linked to the original primary repair or the secondary repair that took place. We therefore pragmatically assumed that all of the data following secondary repair (i.e. the Secondary trial and the Secondary CC) provide the most reliable data for complications and failures following a second prolapse surgery, and these data are applied to all of the secondary repairs in the model.

Table 100 details point estimates and 95% CIs of relative effect sizes used in the model. Uncertainty surrounding the point estimates was characterised using log-normal distributions. Data used to define the distributions are presented as mean and SE of the log estimates. *Table 101* details the point estimates used

TABLE 100 Relative risk parameters used for the economic model

Parameter	Comparison	Time	Mean	Lower value	Upper value	Distribution applied	Mean of logs	SE of logs	Notes/sources
Serious complications									
Relative risk serious non-mesh complications	Standard mesh vs. standard repair	1 year	1.34	0.71	2.52	Log-normal	0.29	0.32	Data from RCT1A
	Biological graft vs. standard repair		1.93	1.07	3.50		0.66	0.30	
Relative risk serious mesh complications	Standard mesh vs. standard repair	1 year	22.52	3.07	165.28	Log-normal	3.11	1.02	Data from RCT1A
	Biological graft vs. standard repair		N/A	N/A	N/A	N/A	N/A	N/A	RR not calculable; see *Table 101*
Relative risk serious non-mesh complications	Standard mesh vs. standard repair	2 years	0.66	0.19	2.30	Log-normal	–0.42	0.64	Data from RCT1A
	Biological graft vs. standard repair		0.49	0.09	2.66		–0.71	0.86	
Relative risk serious mesh complications	Standard mesh vs. standard repair	2 years	24.91	3.4	182.79	Log-normal	3.22	1.02	Data from RCT1A
	Biological graft vs. standard repair		1.22	0.08	19.32		0.20	1.40	
Other complications									
Relative risk other non-mesh complications	Standard mesh vs. standard repair	1 year	0.93	0.48	1.79	Log-normal	–0.07	0.34	Data from RCT1A
	Biological graft vs. standard repair		0.82	0.41	1.62		–0.20	0.35	
Relative risk other mesh complications	Standard mesh vs. standard repair	1 year	N/A	N/A	N/A	N/A	N/A	N/A	RR not calculable; see *Table 101*
	Biological graft vs. standard repair		N/A	N/A	N/A	N/A	N/A	N/A	
Relative risk other non-mesh complications	Standard mesh vs. standard repair	2 years	0.63	0.21	1.88	Log-normal	–0.46	0.56	Data from RCT1A
	Biological graft vs. standard repair		1.1	0.43	2.81		0.10	0.48	
Relative risk other mesh complications	Standard mesh vs. standard repair	2 years	N/A	N/A	N/A	N/A	N/A	N/A	RR not calculable; see *Table 101*
	Biological graft vs. standard repair		N/A	N/A	N/A	N/A	N/A	N/A	
Failures requiring conservative management									
Relative risk failure requiring conservative management	Standard mesh vs. standard repair	1 year	0.85	0.44	1.64	Log-normal	–0.16	0.33	Data from RCT1A
	Biological graft vs. standard repair		0.84	0.44	1.62		–0.17	0.33	
	Standard mesh vs. standard repair	2 years	1.42	0.68	2.99		0.35	0.38	
	Biological graft vs. standard repair		1.13	0.52	2.42		0.12	0.39	

N/A, not applicable.

TABLE 101 Probabilities used in the model where relative risks were not calculable

Variable	Treatment	Time point	Point estimate	Alpha	Beta	Distribution applied	Source
Serious mesh complications[a]	Biological graft	1 year	0	0	255	Beta	RCT1A
Other mesh complications	Standard mesh	1 year	0.0235	6	249		
	Biological graft		0.00392	1	254		
	Standard mesh	2 year	0.0275	7	248		
	Biological graft		0.00392	1	254		

a When no events were reported, a nominal value was included to allow the model to run (i.e. 0.00001).

for data for which relative risks were not calculable. For these parameters, beta distributions were applied, based on count data as in *Table 98*.

Resource utilisation and cost parameters

Costs for use within the economic model are health state specific, based on health-care resource use observed from women experiencing specific events from the trial-based analysis for RCT1A. Mean (SD) costs for women who were experiencing health states were used to populate the economic model. Costs are estimated from the perspective of the UK NHS, and reported in 2014 UK pound sterling (£) values. Costs were based on resource-use data that were reported in the trials. All relevant unit costs underpinning the cost distributions can be found in *Chapters 2* and *5* and *Appendix 6*. Costs of secondary repair surgery are based on intervention costs (microcosted) from the Secondary trial analysis. Base-case costs for secondary repairs in the model were calculated assuming an aggregate of all of the intervention costs from the Secondary trial, regardless of treatment received. Sensitivity analysis explored the impact of assuming that all of the women receive standard repair or all women receive mesh kit for the secondary repair. A further sensitivity analysis used cost estimates from the Primary trial (RCT1A) for those women experiencing a prolapse failure. The latter analysis was based on NHS unit costs, rather than microcosting approach for the base-case analysis of secondary intervention cost. Costs for health states applied to the base-case model were calculated across all of the women who were randomised to RCT1A and were not treatment specific.

The way in which costs for health states were estimated in the base-case analysis depended on whether or not dates of events were available from the trial data set. Costs for events for which no dates of event were available are applied to health states as average costs of treatments incurred over the whole trial follow-up and divided evenly across each model cycle. This includes the cost of conservatively treated failures and women who had no further symptoms (i.e. were stable) in the 'post-prolapse surgery' health state of the model. As many women would not have a clear cure and may still experience symptoms related to prolapse, those women in the 'post-prolapse surgery' health state still incurred a cost. Women categorised as being 'stable' in the 'post-prolapse surgery' health state were defined as those women not reporting conservative management treatments, not having surgery for failure and not experiencing serious adverse effects or any other prolapse-related complications.

Costs of health states for which dates of event were available (e.g. date of surgery for complications or failures) were estimated only for women reporting resource use within 4 months of the event. This allowed a more accurate reflection of resource use that was applied to the limited time in the respective health states for those who experienced complications.

Furthermore, costs included in the model were split between 1- and 2-year follow-up. The justification for this is that the costs of problems incurred over the second year of follow-up are more appropriate for longer-term extrapolation, as they do not include routine follow-up care following surgery and furthermore the patient reported costs in year 2 are unlikely to include trial-based consultations (such as 1-year

prospect follow-up appointment). Costs applied to health states for each model cycle beyond 2 years were assumed to be the same as those incurred between 1- and 2-year follow-up from the trial. Adjustments were undertaken to apply costs to each monthly model cycle.

For the costs of treating serious and other complications, it was assumed that the treatment costs would be similar in terms of resource use for both mesh and non-mesh complications. This is on the basis that to be considered a serious adverse effect, women would have had a substantial contact with health-care professionals and associated treatments. Furthermore, splitting the cost regressions from the trial, based on four different categories (serious mesh, other mesh, serious non-mesh and other non-mesh complications), generated great uncertainty, as a result of small numbers of participants reporting full-cost data within each of these individual groups. Therefore, we pragmatically decided to group costs of serious complications together. A similar approach was taken for 'other' complications.

As a summary, by using estimates of costs from the trial-based analysis in *Chapter 5*, the resource utilisation and costs included in the model are a comprehensive reflection of all resource use, including:

- the interventions, incorporating the surgery, preparations and hospital resource use in theatre, based on operation time, staff time and other additional treatments.
- postoperative resource use (from surgery to discharge), including time on ward, return to theatre, catheterisation, cost of treating any infections, for example UTIs and any other adverse effects
- inpatient admissions (any follow-up operations and length of stay in hospital related to prolapse symptoms, including overnight and day-case admissions)
- outpatient attendances (including all outpatient contacts over the trial follow-up period)
- primary care visits (including GP contacts, occupational therapist, physiotherapist and nurse contacts)
- medications related to treating prolapse and UI symptoms.

Detailed information on how unit costs were developed within the trial are provided in *Chapters 2* and *5*. Costs from the data set were adapted to reflect the additional costs of experiencing prolapse-related events. These health state-specific costs are applied within the model and were assumed to follow a gamma distribution. Unit costs, together with alpha and beta parameters (where appropriate), are presented in *Table 102* in accordance with the specifications outlined by the Treeage software. All costs used in the model were discounted by 3.5% per annum in line with current best practice guidance.[38]

Quality of life

As with the cost data reported above, utility estimates are applied to health states based on mean data for women experiencing a health event from RCT1A. For the base-case analysis, utilities are applied to health states on the assumption that all women in a health state will have equal utility. Utility weights were adjusted to reflect the model cycle length of 1 year and were combined with length of time in a health state to generate QALYs gained. QALYs were then discounted at a rate of 3.5% per annum in line with best practice guidelines. As with costs, the utility of the 'post-prolapse surgery' health state was estimated for those women who were not falling into any of the other health states. Rather than reflecting a health state for which everyone is well or recovered, this state is more 'all encompassing', picking up the QoL impact of prolapse for those not experiencing more major problems. Utility values were also estimated for the women who had complications requiring hospitalisation and had a prolapse failure, requiring reoperation as well as those who had complications that did not need hospitalisations. Furthermore, a separate utility was estimated for those women who were in the 'post-prolapse surgery' health state, but experienced the need for containment or conservative management of their prolapse symptoms. This value was less than for those in a failure health state, but greater than for those requiring surgery for prolapse failure.

All health state-specific utility estimates calculated on the basis of RCT1A (primary repair surgery) were also applied to women who were experiencing a similar health state following second and third repairs. This assumption implies that utilities are not impacted on by the number of previous surgeries experienced. There were insufficient data available from the Secondary trial to estimate health state-specific utilities for

TABLE 102 Cost values used in Markov model health states

Variable	Point estimate (£)	SE (£)	Alpha	Beta	Distribution
Cost of primary repair (standard)	2831	1151	6.05	467.96	Gamma
Cost of primary repair (synthetic mesh)	3128	1042	9.01	347.11	
Cost of primary repair (biological graft)	3258	1279	6.49	502.10	
Cost of further surgery for failure (all secondary repairs: base case)	3112	1289	5.83	533.91	
Cost of further surgery for failure (standard repair: sensitivity analysis)	2790	1295	4.64	601.08	
Cost of further surgery for failure (mesh inlay: sensitivity analysis)	3099	1358	5.21	595.08	
Cost of further surgery for failure (mesh kit: sensitivity analysis)	3522	1100	10.25	343.55	
Cost of further surgery for failure (sensitivity analysis based on Primary trial data)	782	942	0.6891	1134.74	
Cost of surgery for complications (year 1)	1515	948	2.5539	593.20	
Cost of surgery for complications (year 2)	937	1088	0.7417	1263.33	
Cost of being stable in the 'post-prolapse surgery' health state (year 1)	306	475	0.42	737.34	
Cost of being stable in the 'post-prolapse surgery' health state (year 2)	251	524	0.23	1093.93	
Cost of serious complications (mesh and non-mesh; year 1)	1095	1045	1.098	997.28	
Cost of serious complications (mesh and non-mesh; year 2)	858	1079	0.63	1356.92	
Cost of other complications (mesh and non-mesh; year 1)	760	1044	0.53	1434.13	
Cost of other complications (mesh and non-mesh; year 2)	738	1371	0.29	2546.94	
Cost of conservatively managed failures and containment (year 1)	598	709	0.71	840.60	
Cost of conservatively managed failures and containment (year 2)	529	766	0.48	1109.18	

Notes
1. All costs were adjusted to reflect monthly model cycles.
2. Additional surgery costs were applied once only at the time or entering surgery health state.

women who were having a second repair. However, data reported from the Primary and Secondary trial analyses overall (see *Tables 39* and *68*) indicate that women who were having primary and secondary repair had similar EQ-5D scores overall. It is therefore unlikely that, on the basis of currently available data, this assumption has any substantial impact on results.

Table 103 reports the point estimate of all utilities applied to health states within the model. Uncertainty in utility data is characterised and incorporated by sampling from beta distributions for the utility of each modelled health state. Alpha and beta parameters are calculated using the method-of-the-moments approach and the parameters of the distribution are presented in *Table 103*.

Assessment of cost-effectiveness

Cost–utility analysis

The costs and consequences (QALYs) of the different treatment options were estimated for women with an average age of 59 years (the average age of women undergoing prolapse surgery in the primary repair trial) over a 5-year time horizon. The model generated expected values of costs and QALYs, based on a hypothetical cohort of $n = 1000$ women who were having a primary prolapse repair. The base-case model results were calculated using a probabilistic analysis using second-order Monte Carlo simulation with 1000 repetitions. Results from the cost-effectiveness analyses were based on mean estimates of baseline

TABLE 103 Health-state utilities

Health state	Mean value	SE	Distribution	Alpha	Beta	Notes/sources
Treatment failure	0.609	0.296	Beta	1.048	0.673	RCT1A
Complications requiring surgery	0.646	0.454	Beta	0.054	0.030	
Stable in the 'post-prolapse surgery' health state	0.831	0.248	Beta	1.060	0.215	
Serious mesh complications (not requiring surgery)	0.722	0.297	Beta	0.923	0.356	
Serious non-mesh complications (not requiring surgery)	0.722	0.297	Beta	0.923	0.356	
Other mesh complications (not requiring surgery)	0.739	0.314	Beta	0.709	0.250	
Other non-mesh complications (not requiring surgery)	0.739	0.314	Beta	0.709	0.250	
Failure (conservative management)	0.797	0.239	Beta	1.458	0.372	
Baseline utility (standard repair)	0.722	0.245	Beta	1.692	0.652	
Baseline utility (synthetic mesh)	0.711	0.233	Beta	1.980	0.805	
Baseline utility (biological graft)	0.697	0.265	Beta	1.399	0.608	
Baseline utility (all combined)	0.710	0.248	Beta	1.667	0.681	
Additional treatment effect (synthetic mesh): sensitivity analysis only	0.019	0.018	Beta	1.028	53.343	
Additional treatment effect (biological graft): sensitivity analysis only	0.006	0.020	Beta	0.091	14.190	

probabilities, relative effect sizes, utilities and costs that were drawn from the sampling distributions outlined in the above tables of model inputs. Expected values of costs and QALYs were estimated according to the sampled data for each treatment group (standard repair, synthetic mesh and biological graft).

The expected values of costs and QALYs were combined into a single measure of efficiency and reported as incremental costs per QALY gained. These are ratios of the differences in costs of the interventions divided by the differences in the benefits (QALYs). These data reflect the rate of return in QALYs to the quantity of resources used measured in monetary terms. The ICER is used in conjunction with an identified WTP threshold value to determine if the intervention can be judged to be cost-effective. Interventions reporting an ICER of < £20,000–30,000 per QALY gained are generally considered to offer good value for money to the NHS. Interventions that are less costly and generate greater QALYs than a comparator are the dominant treatment, and offer an even stronger case for cost-effectiveness. Results of mean probabilistic results for each treatment group are presented on the cost-effectiveness plane.

Sampling uncertainty is presented in two distinct ways. First, scatterplots of incremental costs and QALYs generated from the simulations are plotted on the incremental cost-effectiveness plane to show the differences in costs and QALYs for synthetic mesh and biological graft, respectively, compared with standard repair. This specifically shows the uncertainty in the respective quadrants of the cost-effectiveness plane.

Second, CEACs are presented alongside the incremental scatterplots. CEACs illustrate the uncertainty in cost-effectiveness outcomes caused by the combined statistical variability in the model's parameter estimates. They show the likelihood that each individual treatment strategy is the most cost-effective use of resources at various threshold values of society's WTP for a QALY gained. CEACs and scatterplots are presented for the base-case and all secondary analyses. Further to these illustrations of cost-effectiveness,

all results (base-case and sensitivity analyses) are also accompanied by an indication of the treatment ranking in terms of the most likely treatment to be cost-effective at a threshold value of WTP of £30,000 per QALY, based on the assessment of NMB.

Deterministic sensitivity analysis

Cost-effectiveness acceptability curves illustrate the sampling uncertainty in the model parameters. However, further uncertainty may exist in the choice of data used to populate the model, the methodological or structural assumptions made or the subgroup analyses considered. Various sensitivity analysis were undertaken to explore the importance of these uncertainties and assumptions.

Parameter uncertainty

In addition to exploring sampling uncertainty in parameters, there is uncertainty regarding the appropriate choice of data that are used to populate the model.

Utilities

Alternative choices of utility weights were available from the trial data for use within the model to generate QALY gains. The base-case analysis is informed by utilities generated for health states in the trial, on the assumption that all women in a health state will experience equal utility. For example, all women suffering a failure will have a utility of 0.609 and all women who are non-symptomatic in the 'post-prolapse surgery' health state will experience a utility of 0.831. Sensitivity analysis explores the impact on cost-effectiveness of applying treatment-specific utilities to all model health states. This analysis is undertaken to reflect that the complete case analysis of the Primary trial indicated some additional incremental utility that was associated with synthetic mesh for all women, including those with complications or experiencing failures over and above women in the same health state for standard repair and/or biological graft. Although the estimates of treatment-specific utility are unexplained by clinical outcomes, and may be biased by substantial missing data, they are included, nonetheless, in the model for completeness. Additional treatment-specific utility is estimated for synthetic mesh and biological graft based on a GLM with adjustment for all model health states and baseline covariates from the trial. The coefficient on treatment is added to the specific health-state utility in the respective arms of the model to estimate a treatment-specific utility for each modelled health state. This reflects the unexplained additional utility, which appears to be experienced by women who are randomised to synthetic mesh in the complete case analysis of the trial-based economic evaluation. It is likely that this analysis would provide an upper bound on the likelihood of cost-effectiveness for synthetic mesh. The additional utility (see *Table 103*) effectively increases the utility of women in all health states for which they received mesh as the baseline treatment. This analysis should be interpreted in the light of the uncertainty in the surrounding trial data.

Costs

As with the trial-based analysis, the estimates of costs to the health services and hence cost-effectiveness of treatments are subject to uncertainty surrounding the intervention cost applied in the model. Therefore, as a sensitivity analysis, we have explored the impact of using the most costly meshes for all mesh repair and the least costly meshes for all mesh repair as plausible upper and lower bounds of the intervention costs.

Furthermore, the costs included in the base-case analysis for treatment failure are generated using the microcosting approach based on Secondary trial data for all of the treatments. A number of alternative estimates are explored in sensitivity analysis, namely assume that all women who were having a secondary repair:

1. get standard repair
2. get mesh inlay
3. get mesh kit
4. incur the costs of treatment failure within the Primary trial (based on the reference costs used to generate the costs of resource use for these women within the trial).

Structural uncertainty

As highlighted in the estimation of model probabilities, there was no reliable evidence on long-term reoperation for prolapse surgery failure. Furthermore, we curtail the model to run for only 2 years for which the most accurate data were available (i.e. the same time horizon as the trial follow-up). This allows us to validate the structure of the model and the predicted results internally against the trial data that were used to generate the model parameters.

The incidence of prolapse is likely to increase with age. The mean age of the participants in the trial was 59 years with a SD of 10 years. The costs and benefits in the model were estimated for 5 years. The sensitivity analysis explores the implications of varying the age of women at the start of treatment and the impact of adopting a longer-term period. Therefore, the starting age was changed to 49 and 69 years, and the time horizon was increased to 10 years. A further exploratory analysis is run over a 30-year time horizon. However, results should be interpreted cautiously, as estimates of time to event are highly uncertain for failures. The model will be updated with data from the 6-year follow-up of PROSPECT and the time horizon extended, based on a more comprehensive time-to-event analysis.

Methodological uncertainty

Discount rates were used at a rate of 3.5% per annum applied to costs and QALYs in the base-case analysis. Sensitivity analysis explores the impact of varying these between 0% and 6% per annum in the sensitivity analysis following best practice guidance.

Utility data in the model are based on trial results and, as such, the utility weights are specific to women suffering from prolapse. As a sensitivity analysis, these utility weights are further adjusted to reflect population norms, which are age adjusted according to the stage of the model, reflecting the fact that utility is likely to fall over time as women get older.

Results

Base-case cost-effectiveness results

The base-case results for the estimates of cost-effectiveness from the probabilistic analysis are presented with treatments ranked in ascending order of costs. Treatment strategies that are more costly and generate fewer QALYs than a comparator are excluded on the basis of absolute dominance and are not considered cost-effective. For the remaining strategies, ICERs are calculated. The treatment strategy with the highest ICER falling under the threshold value is considered the most cost-effective treatment option (note, for the purposes of interpretation, the threshold value of the ICER is considered to be < £20,000–30,000 per QALY gained). The base-case results are presented numerically in *Table 104* and graphically on the cost-effectiveness plane in *Figure 31*.

For the base-case economic analysis, standard repair is considered the most cost-effective treatment strategy, being less costly, with marginally greater QALYs gained. However, differences in QALYs are small in magnitude and results are driven primarily by the additional intervention cost of mesh. Uncertainty in the base-case results is illustrated according to the CEAC presented in *Figure 32*. The probabilities of cost-effectiveness for the base-case results at a threshold value of WTP of £30,000 per QALY gained are 50%, 23% and 27% for standard repair, synthetic mesh and biological graft, respectively. The results of the base-case cost-effectiveness analysis are comparable with the results of the within-trial analysis using the imputed data set in *Chapter 5*. The sensitivity analysis section explores a direct comparison between modelled results over 2 years, and the trial results are reported in *Chapter 5*.

Uncertainty in the individual comparisons of synthetic mesh with standard repair and biological mesh with standard repair is presented in *Figure 33* as scatterplots of the 1000 Monte Carlo simulation estimates of expected costs and QALYs for the respective treatment groups.

TABLE 104 Base-case cost-effectiveness analysis results

Strategy	Cost (£)	Incremental cost	QALYs	Incremental QALY	Incremental cost-effectiveness	Incremental cost-effectiveness (vs. standard repair)	NMB ranking (threshold = £30k)
Standard repair	4811		3.753	0	0		1
Synthetic mesh inlay	5264	453	3.748	–0.0047	Dominated	Dominated	3
Biological graft	5304	492	3.749	–0.0035	Dominated	Dominated	2

Effectiveness measured in terms of QALYs gained.

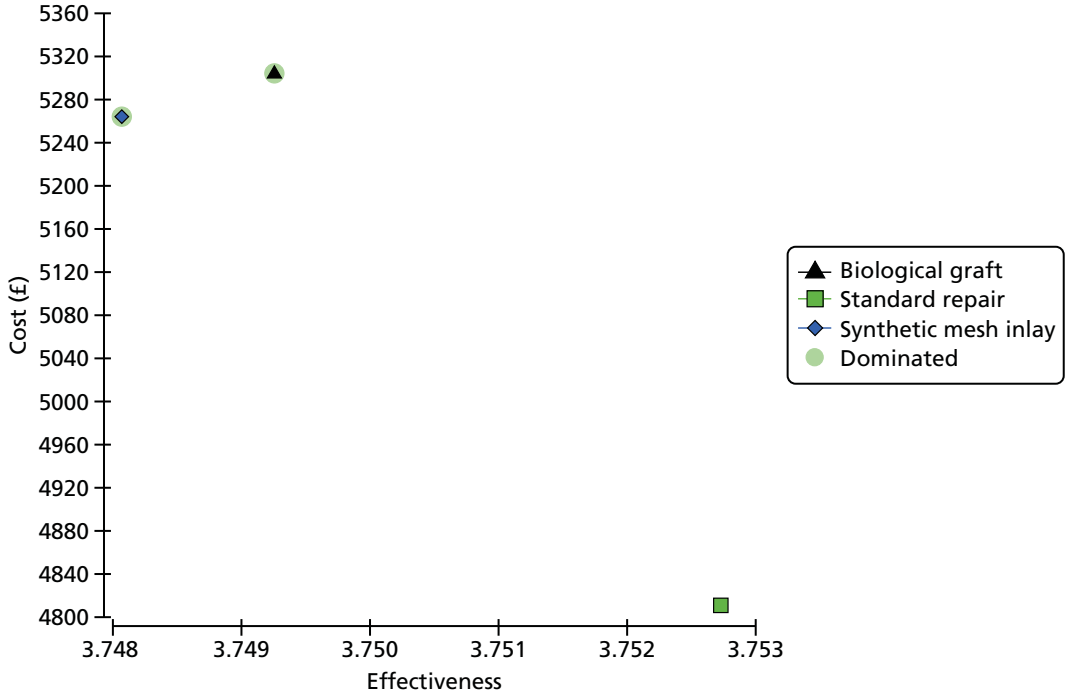


FIGURE 31 Base-case cost-effectiveness plane.

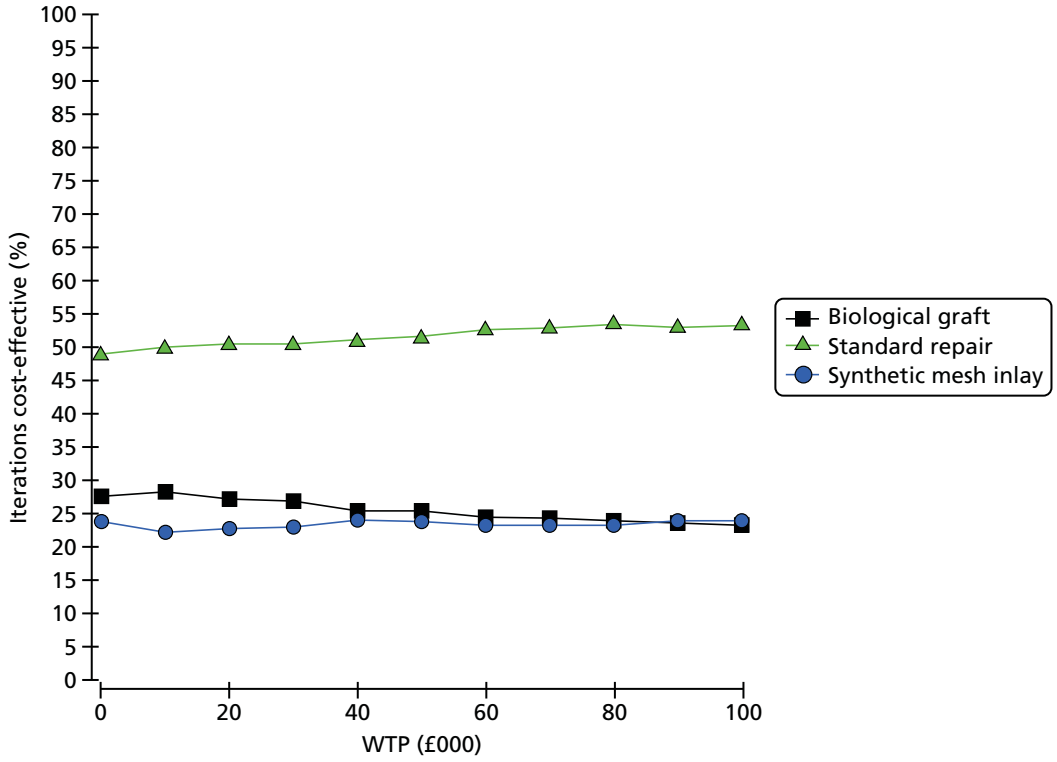


FIGURE 32 Cost-effectiveness acceptability curve.

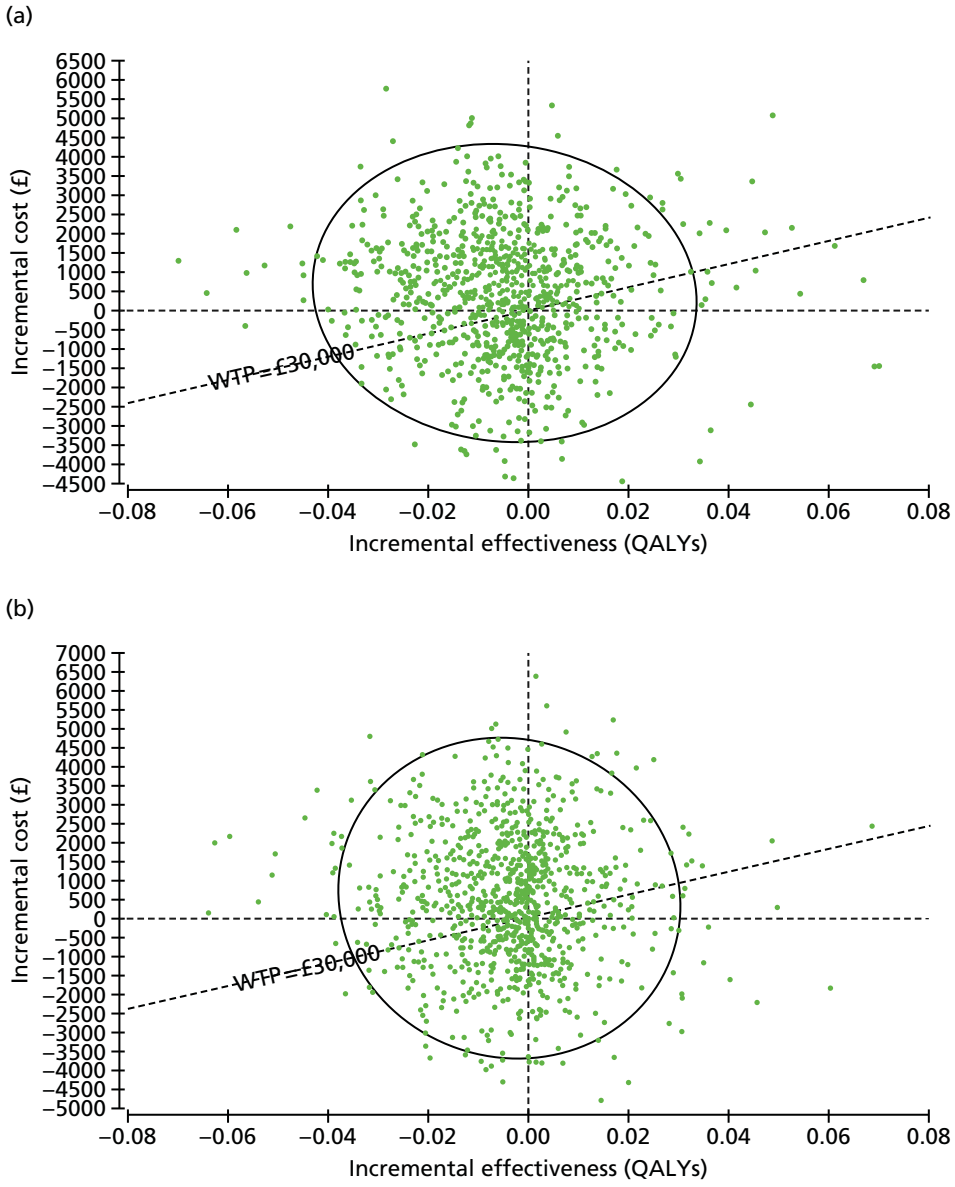


FIGURE 33 Incremental cost-effectiveness for mesh repairs vs. standard repair.

Secondary analysis

Table 105 presents the results of a secondary analysis, which details the cost-effectiveness based on treatment-specific utilities applied to the model. This analysis incorporates the coefficient of treatment effect on QALYs that are generated from GLM models, adjusting for health state in the trial-based analysis model. It essentially adds an additional utility to the synthetic mesh repair for all women in all of the health states, and is more directly comparable with the data seen in the complete case analysis of the trial outcomes reported in *Chapter 5*. Caution should be noted when interpreting the analysis, given that complete case trial data may have been subject to the biases of missing data. The analysis is provided for completeness. The base-case analysis model is more consistent with an imputed data set of missing utility data from the trial. *Figure 34* illustrates the uncertainty in this secondary analysis using CEACs. As with the base-case analysis, a validation check will be explored in deterministic sensitivity analyses running the model over a 2-year time horizon.

TABLE 105 Results of secondary analysis of cost-effectiveness (treatment-specific utilities)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness	Incremental effectiveness	Incremental cost-effectiveness	Incremental cost-effectiveness (vs. standard)	NMB ranking (threshold = £30k)
Standard repair	4811	0	3.753	0	0		2
Synthetic mesh inlay	5264	453	3.829	0.076	5933	5933	1
Biological graft	5304	40	3.769	–0.060	Dominated	29,883	3

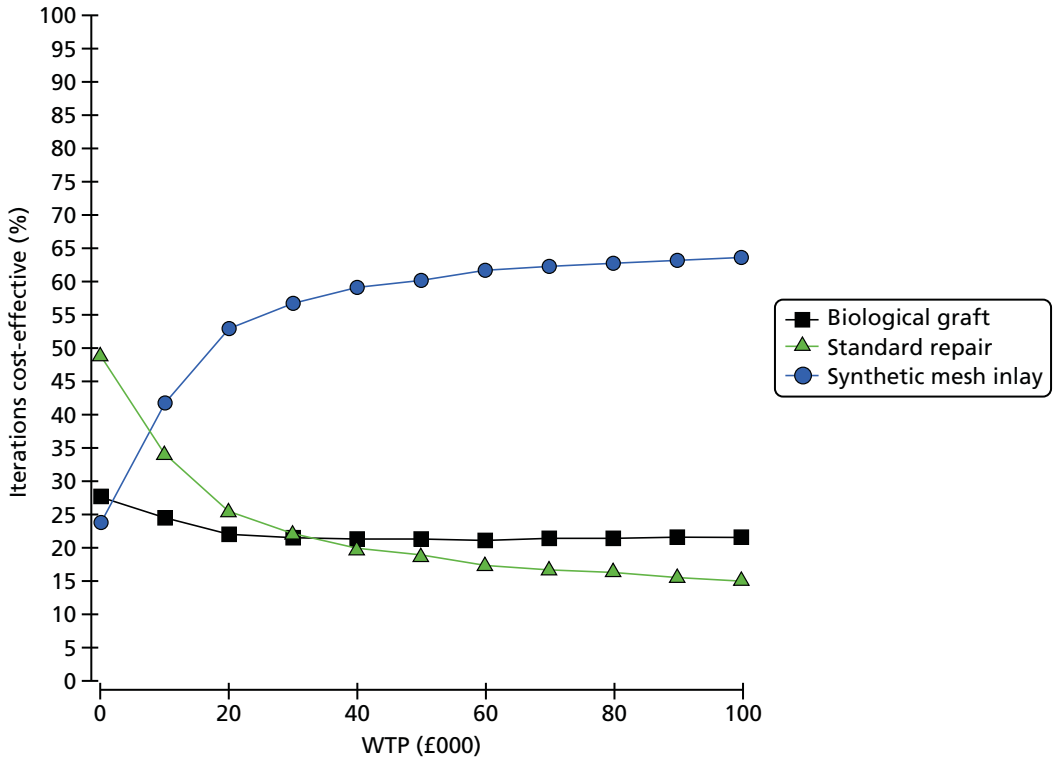


FIGURE 34 Secondary analysis, use of treatment-specific utility.

The secondary analysis including additional incremental QALYs for synthetic mesh indicates a lower ICER and higher probability of cost-effectiveness for synthetic mesh. With an ICER of < £20,000 per QALY gained, there may be an argument for adopting synthetic mesh on cost-effectiveness grounds under this analysis. However, whether or not a decision-maker would consider this as evidence of cost-effectiveness would be determined by whether or not he/she trusts the treatment-specific additional utility gained from synthetic mesh across all of the health states. This analysis may be subjected to biases of missing data that are generated in the trial-based cost-effectiveness analyses. More specifically, the base-case analysis, informed by an imputed data set addressing biases, is more likely to accurately reflect cost-effectiveness. Furthermore, there is some uncertainty in this result, as is illustrated in the CEAC in *Figure 34*. The probabilities of cost-effectiveness at a threshold value of WTP of £30,000 per QALY gained are 22%, 57% and 21% for standard repair, synthetic mesh and biological graft, respectively. The probability of cost-effectiveness of synthetic mesh increases with the higher the threshold value of WTP for a QALY, but never reaches > 65% probability of cost-effectiveness at thresholds up to £100,000 per QALY gained. There is thus substantial uncertainty regarding the most cost-effective treatment strategy across both the base-case and secondary analyses presented here. There is no clear evidence from either model by which to recommend either mesh repair as a cost-effective use of scarce NHS resources. The probability of biological graft being cost-effective is consistently lower than the alternative options, driven by the additional cost of providing the intervention, with no clear gain in QoL over the modelled time horizon.

Results of deterministic sensitivity analyses

The results of the full range of deterministic sensitivity analyses undertaken and described through the methods sections above are outlined in *Table 106*. The results are presented in a similar way to the base-case and secondary analyses outlined above. ICERs are presented incrementally based on ranked treatment options, and also compared with a common baseline comparator (standard repair). The most cost-effective treatment option, following a net benefit approach, under each scenario, is indicated in the final column of the table.

TABLE 106 Results of deterministic sensitivity analyses undertaken

Strategy	Cost (£)	Incremental cost (vs. standard) (£)	Efficiency	Incremental efficiency (vs. std)	Incremental cost-effectiveness	Incremental cost-effectiveness (vs. standard)	NMB ranking (threshold = £30k)
Base-case analysis							
Standard repair	4811		3.753				1
Synthetic mesh inlay	5264	453	3.748	–0.0047	Dominated	Dominated	3
Biological graft	5304	492	3.749	–0.0035	Dominated	Dominated	2
Validation check: running model for a 2-year time horizon (compare with imputed data set in* Chapter 5*)							
Standard repair	3596.75	0	1.584	0.000	0		1
Synthetic mesh inlay	3915.92	319.17	1.582	–0.001	Dominated	Dominated	3
Biological graft	4018.87	422.12	1.582	–0.002	Dominated	Dominated	2
Validation check: running model for a 2-year time horizon with treatment-specific utilities (compare with complete data set in* Chapter 5*)							
Standard repair	3596.75	0	1.584				2
Synthetic mesh inlay	3915.92	319.17	1.614	0.031	10,387	10,387	1
Biological graft	4018.87	422.12	1.586	0.003	Dominated	156,783	3
Extending the model time horizon to 10 years (exploratory only)							
Standard repair	6720.14		6.808				1
Synthetic mesh inlay	7320.80	600.66	6.798	–0.009	Dominated	Dominated	3
Biological graft	7328.99	608.85	6.801	–0.007	Dominated	Dominated	2
Extending the model time horizon to 30 years (exploratory only)							
Standard repair	15055.2	0	19.584	0.000	0		1
Biological graft	15843.08	787.88	19.559	–0.026	Dominated	Dominated	2
Synthetic mesh inlay	15867.61	812.41	19.550	–0.035	Dominated	Dominated	3
Discounting at a rate of 0% per annum for costs and QALYs							
Standard repair	4957.18	0	4.015	0.000	0	0	1
Synthetic mesh inlay	5425.01	467.83	4.010	–0.005	Dominated	Dominated	3
Biological graft	5459.01	501.82	4.011	–0.004	Dominated	Dominated	2

Strategy	Cost (£)	Incremental cost (vs. standard) (£)	Efficiency	Incremental efficiency (vs. std)	Incremental cost-effectiveness	Incremental cost-effectiveness (vs. standard)	NMB ranking (threshold = £30k)
Discounting at a rate of 6% per annum for costs and QALYs							
Standard repair	4718.57	0	3.586	0.000	0	0	1
Synthetic mesh inlay	5161.52	442.95	3.582	–0.004	Dominated	Dominated	3
Biological graft	5205.1	486.52	3.583	–0.003	Dominated	Dominated	2
Model start age = 49 years							
Standard repair	4827.72		3.783				1
Synthetic mesh inlay	5281.99	454.26	3.778	–0.005	Dominated	Dominated	3
Biological graft	5321.29	493.56	3.779	–0.003	Dominated	Dominated	2
Model start age = 69 years							
Standard repair	4770.14		3.678				1
Synthetic mesh inlay	5218.60	448.46	3.673	–0.005	Dominated	Dominated	3
Biological graft	5259.91	489.77	3.674	–0.003	Dominated	Dominated	2
Assuming that the utility of a conservatively managed failure is equal to that of failure requiring surgery							
Standard repair	4811.27	0	3.742	0.000	0	0	1
Synthetic mesh inlay	5263.87	452.6	3.735	–0.007	Dominated	Dominated	3
Biological graft	5303.74	492.48	3.737	–0.005	Dominated	Dominated	2
Imputing a high estimate of mesh material costs (25%)							
Standard repair	4811.27	0	3.753	0.000	0	0	1
Synthetic mesh inlay	5298.12	486.85	3.748	–0.005	Dominated	Dominated	3
Biological graft	5375.74	564.48	3.749	–0.003	Dominated	Dominated	2
Imputing a low estimate of mesh material costs (–25%)							
Standard repair	4811.27	0	3.753	0.000	0	0	1
Synthetic mesh inlay	5229.62	418.35	3.748	–0.005	Dominated	Dominated	3
Biological graft	5231.74	420.48	3.749	–0.003	Dominated	Dominated	2

Interpretation of sensitivity analysis results

Model validation checks

As a check on the face validity of our model results, we have undertaken two analyses of the model over a 2-year time horizon. Given that the trial-based follow-up was of 2 years' duration, it is only reasonable to assume that the model would reasonably accurately reflect the data that were seen in the trial. Therefore, the model was rerun over a 2-year time horizon to determine how closely the results matched the trial analysis. It should be noted that this analysis was conducted to check model face validity results and not as a direct attempt to replicate the trial-based analyses. An analysis in which health-state utilities were not treatment specific matches the conclusions and cost-effectiveness rankings of treatments seen in the imputed data set for the Primary trial analysis. Adding an additional treatment-specific utility to the model produces rankings similar to those found in the complete case analysis. This reflects the conclusions of the trial-based analyses in which imputed data sets showed lower probabilities of mesh repairs being cost-effective than in complete case analysis. The important note to take from this analysis is that the direction of effect is the same, and conclusions remain unchanged from those estimated in the trial analysis. This is reassuring for the internal validity of the model structure. The longer-term follow-up of the trial data will provide an opportunity to validate the projections of long-term failures and complications up to 6 years of follow-up.

Other sensitivity analyses

For a range of sensitivity analyses undertaken, the base-case model conclusions remain unchanged. Based on current data and projected over 5 years, there is little chance of mesh being cost-effective. This is, in part, due to the additional cost of mesh procedures and also to the additional costs and QoL decrements that are associated with treating mesh-related complications. As a result, there would need to be a substantial fall in mesh cost and/or a substantial change in failure rates over the extended follow-up period before mesh would be considered a cost-effective use of scarce NHS resources. Despite the additional cost of biological grafts, even relative to synthetic mesh, there is roughly equal chance of either mesh being cost-effective. This is driven in the model by higher surgery rates for complications in the synthetic mesh group than with biological grafts. In order to be considered cost-effective at a WTP of £30,000 per QALY gained, the total intervention cost would need to reduce by 20% and 21% for synthetic meshes and biological grafts, respectively. The price of the mesh products would be required to fall by a substantially higher percentage in order to achieve this overall percentage reduction in total intervention cost. Furthermore, given current projections of complications over 5 years, the true failure rate for standard repair would need to be substantially greater than synthetic mesh and biological graft at 5 years for either mesh to become definitively cost-effective. In order to fully understand the cost-effectiveness of mesh, more information is required on the longer-term trade-offs between the additional risk of complications (particularly for synthetic meshes) and any longer-term differences between treatment arms regarding failure rates.

Discussion

Summary of main findings

The base-case analysis indicates that standard repair costs less and has only marginally higher QALYs than both synthetic mesh and biological graft procedures. The base-case ICER therefore indicates that standard repair is the dominant treatment strategy. These results are similar to those of the imputed data set for the within-trial analysis in *Chapter 5*. The cost-effectiveness results are driven primarily by the additional cost of mesh materials. Considering that decision-makers would be willing to pay up to £30,000 for a QALY gained, there are 23% and 27% chances of synthetic mesh and biological graft being considered to be cost-effective, respectively.

The secondary analysis that takes into account the treatment-specific utilities indicates a more favourable result for synthetic mesh. This analysis is most comparable with (and developed using) the complete case analysis of cost and QALY pairs from the trial. This analysis includes the additional unexplained health-related

QoL that is evident in the complete case trial analysis, which increases the likelihood of synthetic mesh being cost-effective. This analysis provides a likely upper bound on the likelihood of mesh being cost-effective. Under the assumptions of this analysis, adding treatment-specific utilities to health states, synthetic mesh and biological grafts remain more expensive than standard repair. However, synthetic mesh also generates greater QALY gains. The incremental cost per QALY gained when synthetic mesh is compared with standard repair is £5933. When considering that society's maximum WTP for a QALY gained might be £30,000, there is 22% chance that standard repair would be considered to be the most cost-effective treatment option, a 57% chance for synthetic mesh and a 21% chance for biological graft. Therefore, despite the potentially favourable ICERs, the reader's attention is drawn to the uncertainty surrounding the most cost-effective treatment option.

These analyses indicate two plausible estimates of incremental cost per QALY gained, and each are surrounded by considerable uncertainty regarding the optimum treatment strategy for primary prolapse repair. Owing to the additional costs of synthetic mesh and biological graft repairs, there is no strong evidence from any of the considered economic models to recommend mesh as a cost-effective use of scarce NHS resources, based on 2-year data. There would need to be a substantial increase in the failure rate of standard repair over the longer term, relative to mesh, before the mesh repairs would become cost-effective.

The results of the deterministic sensitivity analysis were similar to the base-case analysis, indicating that the results were not particularly sensitive to choices around model structure, methodological assumptions or the choice of data to populate the model. The cost of standard midline repair was always less than that of both synthetic mesh and biological graft. The differences in QALYs were small throughout all the analyses undertaken with no treatment strategy offering a clearly superior outcome in terms of QALYs gained. Scatterplots of incremental QALYs show substantial uncertainty. There was also uncertainty in overall modelled costs, but to a lesser degree than QALY outcomes.

Strengths

A strength of this analysis is that it is the first analysis that reports a model that is populated using data derived from a large RCT and the model parameters – such as benefits, costs, reoperation and complication rates – were derived from the trial participants. The study also included women who were having secondary treatment and it was undertaken from a UK perspective.

Limitations

Modelling the cost-effectiveness analysis was a challenge as a result of the lack of long-term data, although the trial participants were followed up for 2 years. The second and third prolapse treatment costs and outcomes were informed by the results of the Secondary trial, which was based on women who had already had a prolapse treatment. The costs and outcomes of women who had second and third treatments were based on an aggregate of the three available treatments, as there was no difference in costs or outcomes. This was considered appropriate as the number of women in this trial was small. The model had a provision for only two follow-up surgeries, which may be considered to be an overestimation in a 5-year follow-up period. Evidence from the Secondary trial suggested that, on average, women had prolapse symptoms or are bothered by prolapse for at least 2 years before they had surgery. In addition, there were some women in the Secondary trial who had a new prolapse operation, although the numbers were quite low – about 5% – so the additional costs would be expected to be low as well.

It should be noted that in terms of comparison with the clinical trial data set, the model projections performed reasonably well. However, caution should be noted when comparing the analyses directly as the model is based on projections and assumptions from the trial data and does not exactly replicate the trial analyses. Over a 2-year time horizon, the most valid data come from the economic evaluation alongside the randomised trial. However, 2-year follow-up in itself is not particularly meaningful, and cost-effectiveness conclusions overall should be drawn on the best possible projection of longer-term costs and QALYs generated using the modelling approach.

We present results from the decision-analytic model as incremental cost per QALY gained. Given recommendations for best practice and requirements for decision-making bodies, such as NICE, cost per QALY is the most appropriate method by which to judge the value of new technologies to NHS decision-makers. We initially planned to run the model on the basis of cost per woman cured. However, given the low proportion of women completely symptom-free across the trial groups at 2 years, such an analysis would not be meaningful. Furthermore, given difficulty in reaching a consensus on what constitutes 'cure', we are unable to estimate the model for cost per symptom-free woman: such an analysis would lead to misleading recommendations to decision-makers. We would encourage decision-makers to draw opinions on economic value from the cost-per-QALY analyses that are presented in the decision modelling chapter (see *Chapter 9*).

The within-trial results highlighted the uncertainty on the costs and QALYs, and this was reflected in the modelling analysis. Several assumptions had to be made because of the lack of data. Although there were data on the number of participants who had further treatment, there were no data on the specific additional surgery the women had.

Generalisability of results

The base-case analysis results are similar to those that have been previously published;[64] however, the analysis that uses treatment-specific utilities differs, as they indicate that synthetic mesh has a > 50% chance of being considered to be cost-effective at a society's WTP threshold of between £20,000 and £30,000. However, these results have to be treated with caution, taking into account that there is great uncertainty.

Future research

The modelled results project 2-year outcomes over a longer time horizon. However, there is no information to accurately predict long-term trends and the model essentially extrapolates trends of surgery for failure and complications over time. This may or may not be an accurate reflection of true failure and complication rates. It is therefore imperative that further research from the long-term follow-up of the PROSPECT trial is included before a definitive decision on cost-effectiveness can be reached. The current model time horizon of 5 years is also too short to definitively determine cost-effectiveness, which should be estimated over an individual's whole lifetime. However, insufficient data were available at 2 years to make this projection. Furthermore, there were insufficient data available in the literature to supplement the trial data regarding differences in failure rates and complications between the randomised arms over a longer time horizon. The PROSPECT long-term follow-up will therefore be used to validate or refute the modelled projections of failures and complications, and will provide more accurate data of time to failure/complications in order to further extend the modelled time horizon. At this point, there is likely to be a much clearer knowledge of the true longer-term trade-offs between complications and failure rates for meshes compared with standard midline repairs for women with primary prolapse repair.

Once the initial stage of longer-term follow-up has been completed, more accurate data will exist to make longer-term model projections, especially around failure and complication rates. Once 6-year follow-up is complete, we will conduct a value of information analysis to determine if evidence at this point is sufficient to make recommendations to decision-makers on cost-effectiveness grounds or if further research is worthwhile. If we determine positive expected value of perfect information at this stage, we will use expected value of partial perfect information methods to determine the model parameters that require more, longer-term data to definitively determine the most cost-effective prolapse surgery strategy for women who are having their first primary prolapse repair.

Conclusions

Over the 5-year follow-up presented in the model, depending on the utilities used, there was conflicting evidence regarding the most cost-effective treatment for women with prolapse. Although the outcome data were extrapolated to 5 years, there is still uncertainty about the long-term failure rates and complications of all the treatments for both primary and secondary prolapse. As stated in the within-trial analysis summaries, there is need for longer-term follow-up to better inform decision-makers.

Chapter 10 Overarching discussion

Summary of findings

The PROSPECT Study has shown that, compared with standard repair, there is no benefit in the first 2 years after surgery to women from the use of synthetic mesh inlay or biological graft inlay in the treatment of women who were having their first repair of an anterior or posterior pelvic organ prolapse. In the trial among women who were having a secondary (repeat) repair in either compartment, there was not enough evidence to say whether synthetic non-absorbable mesh inlay or mesh kit was any more or less effective than standard repair in the first 2 years after surgery, because the sample size was too small to be conclusive.

However, there was clear evidence that the majority of women did report improvement in their prolapse symptoms, QoL and other aspects of urinary and sexual function, whichever operation was chosen. The majority of women felt that their health was better after surgery, and this effect was sustained for at least the first 2 years after surgery.

Adverse effects were rare, other than those related to mesh exposure. Importantly, there was no excess risk in the short term to women from the more complex surgery involved in the use of mesh (e.g. extra dissection to insert and fix the mesh inlays): the incidence of 'expected' adverse effects, such as infection and bleeding, was similar in all of the groups of women, and infrequent.

Both synthetic mesh inlay and biological graft inlays were more costly than standard repair for women who were having their first pelvic organ prolapse repair. There was no evidence of differences between treatments in terms of use of health services over 2 years of follow-up. Despite some uncertainty in cost-effectiveness, there was no clear compelling evidence to recommend mesh as a cost-effective use of NHS resources based on the analysis at 2 years. Based on the results of a decision-analytic model to extrapolate trial data over a longer (5-year) follow-up, there was insufficient evidence to recommend either mesh repair. The results of the longer-term modelling suggest that the longer-term rate of failure of standard repair would need to increase substantially relative to synthetic mesh inlay of biological graft inlay before either may be considered cost-effective.

Strengths and limitations

Pragmatic study

One of the strengths of the PROSPECT Study was its pragmatic reflection of actual practice in a representative sample of women under the care of UK gynaecologists carrying out prolapse surgery across a large number of hospital settings. This was reflected in the range of concomitant surgery, and in our ability to differentiate between women who were having a first or a repeat repair in a particular compartment, defined using the most up-to-date recommendations for nomenclature.

Validated outcome measures

We used validated, reliable and reproducible instruments to measure outcomes that were relevant and important to women. Our primary outcome, the POP-SS, comprised seven symptoms that are commonly reported by women who have prolapse. Our findings were robust whether we used the composite score or the individual symptoms. The other measures of pelvic floor dysfunction (urinary, sexual, bladder or bowel) provided similar findings.

The use of the validated and standardised POP-Q system to objectively measure prolapse provided some external validity to the trial, in that it is the most commonly reported outcome in the other RCTs that have examined prolapse surgery.[18] We found that although post-surgery measurements were, on average, better than before, 15% of women who had undergone a primary repair and 10% of women who had a secondary repair still had a prolapse outside the hymen. This calls into question what can be defined as 'cure' of prolapse. We agree with Barber *et al.*[62] – that the important perspective in relation to 'cure' is the woman's view, encapsulated in her own report of prolapse symptoms, their effect on QoL and her satisfaction with the overall outcome of surgery, rather than the physical presence of the prolapse.

The mismatch between objective POP-Q and women's symptoms has been noted by other researchers.[3,60] Data from PROSPECT will provide a rich data source for methodological research into which outcomes matter to women, the relationship between different outcomes, the size of effect, which is important in clinical terms and hence which outcomes most truly reflects success and failure.

Use of Pelvic Organ Prolapse Quantification and redefinition of 'failure'

The POP-Q system classes measurements from –1 cm inside the hymen to 1 cm as stage 2.[27] We and other researchers[28] have pragmatically used a measurement of > 0 cm to indicate objective failure of treatment, although recognising that women with worse anatomical findings may not have symptoms and vice versa (women with objective 'cure' may still have prolapse symptoms). This has resulted in a division of Bump *et al.*'s stage 2 into 2A (leading edge at the hymen or less, 0 or –1 cm) and 2B (leading edge beyond the hymen, > 0 cm).[27] However, the clinical findings of PROSPECT (in terms of success/failure of treatment) would have been the same whichever stage of prolapse was chosen as the cut-off.

However, we would encourage the gynaecological community to consider what level of prolapse constitutes 'normal vaginal wall laxity' and which level of prolapse could be considered as clinically significant. The need for surgery should depend not only on objective findings, but also on the woman's clinical symptoms and their effect on QoL, and the chance that surgery is likely to improve them (rather than improving the anatomical appearance of the prolapse).

Trial design and conduct

We conceived the trial to use primarily a randomised controlled design for maximum scientific reliability. We designed the study to include CCs of women who were unwilling to be randomised or whose surgeons were unwilling to randomise them. This provided generalisability but also simplified the process of recruitment in the centres (in that all women were potentially eligible for one part of the study). The very high recruitment rate (88% of all eligible women) justified our approach.

We used a secure and unbiased third-party method of randomisation that utilised minimisation to take account of predictable confounding factors, such as planned concomitant surgery. Allocation was minimised according to:

- the woman's age (< 60 years or ≥ 60 years)
- type of prolapse being randomised (anterior, posterior or both)
- need for a concomitant continence procedure (e.g. TVT) or not
- need for a concomitant upper vaginal prolapse procedure (e.g. hysterectomy, cervical amputation, vault repair) or not
- surgeon.

Web-based randomisation and data entry further simplified the recruitment and follow-up processes.

Our high recruitment rates were matched by high retention rates (withdrawals were rare and non-response to questionnaires was around 10%). We used evidence-based retention strategies, such as newsletters and telephone calls, to maintain engagement with our participants.

Blinding of care providers and participants

It was not possible to blind the surgeon to the randomised procedure. Once in theatre, the surgeon could, and sometimes did, choose to carry out a different operation to that randomised or that which was originally planned, if this was clinically indicated. This pragmatic approach reflected real-life practice.

The women, on the other hand, were asked if they would be willing to remain blinded to the surgery to which they had been randomised, and that which was actually carried out, unless there was a clinical need to reveal this information. The majority of the women agreed to this. As the primary outcome was their self-reported prolapse symptoms by questionnaire at intervals after surgery, this would be expected to reduce the chance that they might report 'better' or 'worse' symptoms or QoL, depending on their attitude to the surgery that they actually received.

Blinding of outcome assessors and participants

Data entry from the questionnaires was carried out by staff blinded to randomisation and surgery actually conducted, using study numbers only to identify participants. The clinical examination at 1 year was carried out by staff similarly blinded, before looking at the medical notes to find out what had been done. The women were asked not to disclose any information that they knew about their surgery before they had been examined. This process was successful in 90% of cases for blinding to randomised allocation, and in 83% of cases for blinding to treatment received.

Generalisability

The inclusion of around 1500 non-randomised women in a CC had a number of advantages. By and large, the populations in the RCTs and CCs were similar for both the women who were having primary surgery and those who were having repeat surgery, suggesting that the findings from the randomised women are generalisable to the larger population of women who are having prolapse surgery in the UK. As the outcomes in the CCs were similar to those of the comparable randomised women, we conclude that the findings of the RCTs are generalisable to the whole population of women who are having prolapse surgery in the UK.

The inclusion of the CCs also increased the power of the study to identify the background rate of adverse effects in women who are having prolapse surgery. In particular, more women who were having repeat surgery entered the non-randomised group, sometimes by their own choice to have mesh and sometimes because their surgeon felt that mesh was indicated. Despite this, their outcomes were broadly similar to those of the women who were randomised.

Primary compared with secondary (repeat) surgery

When we planned PROSPECT, we found a range of views among gynaecologists about the value of mesh and its place in women who are having prolapse surgery. In general, those who were less likely to use mesh thought that it might be of more value in women who had already had a failed previous repair, as it was known that those women were even more likely to have a failed repeat repair.[4] This led to our decision to run two separate RCTs, according to whether the compartment had previous surgery (secondary) or not (primary). We did find important demographic differences between these populations of women (see *Chapter 3*), justifying our decision to run two trials.

Although we knew that there would be fewer women available for the Secondary trial, the numbers were further reduced by our strict definition, such that some women who had undergone prolapse surgery in the past, but in a different compartment, were deemed to be eligible for the Primary trial. In addition, the women and their surgeons were less open to randomisation, with 61% declining randomisation but being willing to enter CC2.

For these reasons, we are unable to be conclusive about the findings in the Secondary trial. In particular, our assumption that these women were more likely to require non-absorbable mesh to provide a stronger repair cannot be reliably confirmed or denied.

Analysis by strata

We found that some surgeons were not able to randomise women to all of the three arms in each trial, for reasons including personal preference, availability of mesh or training in a particular technique. As a result, the Primary trial consisted of three strata (a three-arm trial and two two-arm trials comparing standard with synthetic mesh and standard with biological graft). Similarly, the Secondary trial consisted of three strata (a three-arm trial and two two-arm trials comparing standard with synthetic mesh and standard with mesh kit). An advantage was that this allowed extra surgeons and centres to participate, thus boosting the potential population and shortening the trial.

A limitation is that, in order to calculate unbiased estimates of treatment effects, we could use only two out of three strata in any analysis (strata A + B for comparisons with synthetic mesh, strata A + C for comparisons with biological graft). However, the power of the analysis was reduced by only a modest amount because the three-arm stratum A was the largest stratum in both the Primary and Secondary RCTs and was used in every analysis.

Economic analysis

A full economic evaluation was conducted alongside the Primary and Secondary trials, following best practice guidelines for economic evaluations. Furthermore, a longer-term decision-analytic model was developed to extrapolate the trial outcomes over a longer (5-year) time horizon. The decision-analytic model projects longer-term failure and complications rates for each treatment based on the data observed in the trial. Although this allows for a longer-term assessment of cost-effectiveness, the data used to populate the model may not reflect the true longer-term rates of complications and failures. The data presented from the model are a best estimate of future cost and QALY implications for primary prolapse repair treatments based on the current data available. Longer-term follow-up data from PROSPECT will be used to validate the model structure and parameters. These data will inform an updated model, which will project cost-effectiveness results over a much longer time horizon. This will enable a more comprehensive assessment of lifetime costs and outcomes of prolapse surgery.

A limitation of the economic analysis is that there were insufficient data to model the longer-term costs and outcomes specifically relating to secondary prolapse repair. Further information is required to robustly assess any differences in long-term cost-effectiveness of mesh for women who were having a secondary prolapse repair.

Need for further research among women requiring treatment for secondary prolapse

As noted, our findings for women who were having repeat surgery were inconclusive because of the small sample size. Although we expected 3 in 10 of the women to be eligible for the secondary group, the numbers were lower because our strict definition of 'repeat surgery' (according to the most recent classification this is now defined as 'in the same compartment'[57]) and because fewer than expected were willing to be randomised. Those women have a higher risk of failure than those having their first procedure.[4] A further RCT among women who have already had a previous failure in a particular compartment is therefore needed so that we can offer them sound evidence-based advice (see also *Chapter 11*).

Meaning of the study

Comparison with the most recent Cochrane review

PROSPECT has shown that, in the first 2 years after surgery, there is no benefit to women who were having their first repair either in terms of prolapse symptoms or anatomical cure from the use of synthetic mesh, biological graft or (less conclusively, because of smaller sample size) mesh kit to reinforce a standard anterior or posterior repair. This contradicts the conclusions of the most recent Cochrane review in 2013,[18] which found both fewer women with prolapse symptoms with synthetic mesh (RR 1.44, 95% CI 1.15 to 1.80; nine RCTs including 930 women) compared with standard repairs and less objective prolapse (in terms of anatomical measurements: RR 2.45, 95% CI 1.64 to 3.67; 11 RCTs, 1150 women).

On the other hand, our findings concur with the uncertainty of the 2013 evidence[18] for a difference for biological grafts (RR for number of women with symptoms 1.03, 95% CI 0.61 to 1.75; three RCTs, 400 women; RR for objective failure 1.35, 95% CI 0.74 to 2.46; six RCTs, 560 women) but with narrower CIs.

Comparison with other randomised controlled trials of no mesh compared with mesh use in prolapse repair

We have now updated the findings of the 2013 Cochrane review[18] by adding information from a further 13 RCTs and two studies, which updated information on already included RCTs. This new systematic review now includes information from 4232 women, in addition to the current PROSPECT data from 1348 women who were having primary surgery and 154 having repeat surgery (5734 women in total; see *Appendix 7*).

The new message from this updated review is that, including additional evidence from the 13 new RCTs and PROSPECT, the overall result no longer favours synthetic non-absorbable mesh inlay in terms of the number of women with prolapse symptoms [(36% after standard repair vs. 30% after mesh inlay; RR at 1 year 1.17, 95% CI 1.00 to 1.37; six RCTs; 1210 women; see *Figure 35*); (31% compared with 28%; RR at 2 years 1.11, 95% CI 0.94 to 1.33; six RCTs, 1175 women; see *Figure 36*)]. However, mesh inlay still seemed to be better than standard repair in that fewer women had objective residual prolapse [(27% after standard repair vs. 11% with mesh inlay; RR at 1 year 2.79, 95% CI 1.83 to 4.26; 16 RCTs; 2360 women; see *Figure 37*); (44% vs. 19%; RR at 2 years 2.53, 95% CI 1.52 to 4.22, eight RCTs, 700 women; see *Figure 38*)]. This difference in objective findings did not translate into a greater number of women who were having further prolapse surgery by 2 years (5% after standard repair vs. 4% with mesh inlay; RR 1.23, 95% CI 0.85 to 1.79; 13 RCTs, 2238 women; see *Figure 39*).

In contrast, findings for mesh kits were conflicting. At 1 year, fewer women had prolapse symptoms after standard repair (35% vs. 48% after mesh kit; RR 0.73, 95% CI 0.59 to 0.90; three RCTs; 495 women; see *Figure 35*), but at 2 years the numbers were small and the difference was not statistically significant (RR 1.10, 95% CI 0.79 to 1.53; two RCTs; 151 women; see *Figure 36*). Although fewer women had symptoms at 1 year, more women had objective prolapse after standard repair (46% vs. 11% after mesh kit, RR 3.67, 95% CI 2.07 to 6.52; four RCTs, 342 women; see *Figure 37*) and more women required further prolapse surgery (5% vs. 1.6% after mesh kit; RR 3.65, 95% CI 1.51 to 8.86; five RCTs, 746 women; see *Figure 39*), although the total number of women needing surgery ($n = 24$) was small. These counterintuitive results underline the lack of concordance between subjective and objective prolapse outcomes.

There were no new trials testing the effects of biological grafts. The inclusion of data from the PROSPECT Primary trial (see *Chapter 4*) has made little difference to the findings. They show either no benefit from the use of biological grafts or marginally favour the no-graft standard repair (e.g. number of women with prolapse symptoms at 2 years; 28% vs. 35% with graft; RR 0.78, 95% CI 0.63 to 0.97; three RCTs, 737 women; see *Figure 36*).

It is difficult to understand why meta-analysis from numerous smaller trials should have previously demonstrated advantages from synthetic mesh in terms of symptoms and anatomical findings in contrast with the findings from PROSPECT. It may be that a single large trial that is free from risk of bias is more powerful than a meta-analysis of many smaller trials of cumulatively equal size (Professor Adrian Grant, HSRU, November 2014, personal communication) but other factors may play a role.

Women requiring repeat prolapse surgery

The previous RCTs included in the most recent Cochrane review[18] rarely reported their outcome data separately according to the crucial baseline characteristic of repeat surgery. Even when they did, they identified potentially eligible women as having had 'any previous prolapse surgery' rather than our stricter definition of 'in the same compartment'. Therefore, it is likely that the data from those RCTs cannot be

combined with those from the secondary group in PROSPECT because of the heterogeneity in baseline classification. This is further discussed in *Chapter 11*.

Long-term follow-up

Given that surgical failures requiring repeat repair occur, on average, 12 years after initial surgery, longer-term follow-up is required to determine true effectiveness, cost-effectiveness and other sequelae of mesh or graft insertion. We are funded to follow PROSPECT women in the longer term (for 6 years after surgery in the first instance) to establish the true incidence of surgical failure and long-term adverse effects.

Adverse effects and mesh complications

Complications from mesh insertion were few and, in general, resolved within the first 2 years. It remains to be established if there are important long-term adverse effects from the use of mesh or if these may still be offset by a reduction in the need for repeat prolapse surgery in the long term.

Although there were no differences in outcomes related to pain or dyspareunia (see *Tables 22*, *23*, *29*, *57*, *58* and *64*), the effect of mesh or indeed non-mesh prolapse surgery on long-term pain requires quantitative and qualitative evaluation. This is hampered by the lack of effective outcome measures for pain. Ideally, the issue of chronic pain should now be addressed prospectively using standard definitions and allowing assessment of the degree of pain, as has also been noted in the context of hernia surgery.[65]

Conclusions

In summary, there is no clear superiority of the synthetic mesh, biological graft or mesh kit over standard repair in the first 2 years after surgery. Unless there is a significant decrease in the reoperation rates for failure in the medium or long term in the mesh or graft arms relative to standard repair, it is unlikely that any type of mesh or graft is going to be cost-effective, given the excess cost over standard repair and the excess cost of treatment for the adverse effect of mesh exposure or extrusion. Long-term follow-up is now ongoing.

Chapter 11 Conclusions and recommendations

The PROSPECT Study includes the largest multicentre RCT evaluating the use of mesh in women who are having a first anterior or posterior prolapse repair, and also separately in women who are having repeat operations. It has comprehensively assessed both the clinical effectiveness and cost-effectiveness of the use of mesh within the UK NHS, and the results are generalisable to the community of women with these types of prolapse.

The 1- and 2-year results have demonstrated that there is no extra clinical benefit from mesh in women who are having their first repair in terms of prolapse symptoms or anatomical resolution of the prolapse. The incidence of adverse effects (other than mesh exposure) was similar in women who had surgery with or without mesh or graft. The findings on prolapse symptoms, anatomical prolapse and adverse effects are not conclusive in women who are having a repeat repair, as a result of the smaller sample size, but are of the same order.

Equally, however, the short-term result of the prolapse surgery studied for all of the groups was good in terms of relief of prolapse symptoms and satisfaction rates, achieved in > 80% of women, although 8% in the primary RCT and 10% in the secondary RCT had a complication that was classified as serious in the first year (excluding mesh exposure). These benefits were retained to 2 years, but long-term follow-up of the participants in PROSPECT is essential to identify the need for repeat or further prolapse surgery and the development of new adverse effects.

Implications for practice

Based on the findings of PROSPECT, there does not appear to be a reason to suggest to women who were having their first repair that mesh can improve their outcomes in the first 2 years after prolapse surgery. However, there may be yet unidentified benefits in the medium or longer time span in terms of reduced need for repeat prolapse surgery. Long-term follow-up is required to identify any potential benefit and, crucially, late presentation of adverse effects that may affect women's health and QoL. Assessment of any longer-term trade-offs between the need for reoperation and longer-term adverse effects will ultimately inform decision-makers with regard to the most cost-effective treatment strategy.

Because of the risks of any surgery, women should be advised to first explore other effective means to manage their prolapse symptoms before resorting to surgery. These may include modification of lifestyle factors, such as obesity and heavy lifting, the use of pessaries, PFMT and other forms of exercise, and, for postmenopausal women, local oestrogen treatment.

Implications for research

The evidence consistently shows that 30% of women who have surgery for prolapse will require further prolapse surgery in either the same or a different compartment in the long term. Long-term follow-up information from PROSPECT will provide detailed prognoses for different clinical groups of women, such as those who were having a first or repeat repair, who did and did not have combined prolapse surgery in more than one compartment, and with or without concomitant surgery. The longer-term follow-up data will provide crucial evidence to more definitively determine the most cost-effective treatment strategy for primary prolapse repair.

Treatment for women with secondary prolapse

Research is required to determine whether the need for further surgery can be reduced if a first prolapse operation fails. Those women have a higher risk of failure than those having their first procedure, and had

a higher symptom score before surgery, indicating worse prolapse symptoms (see *Table 8*). A further RCT among women who have already had a previous failure in a particular compartment would therefore be needed so that we can offer them sound evidence-based advice. However, given the results of PROSPECT to date, strong doctor/patient preferences and the current political and medico-legal climate, it is unlikely that any UK surgeons would be willing or able to 'continue' the Secondary trial. It may be that in other countries (such as France) where mesh is still widely used, a new trial would be feasible.

It is also possible that the long-term follow-up of PROSPECT, which includes CC women who were not randomised, will provide more detailed information on the outcomes of women who have more than one operation. Previous research has rarely focused on this group of women. Arguably, their higher level of symptoms and risk of failure might make them more tolerant of a higher risk of adverse effects if their overall outcomes can be improved.

An alternative approach would be an individual patient data meta-analysis of existing mesh surgery trials, which would require international co-operation from the triallists and participants who were randomised in earlier trials. The updated evidence (see *Appendix 7*) contains information from about 5700 women (of whom 1500 are from PROSPECT) who were randomised to standard repair compared with a repair plus mesh or graft. Given that approximately 30% would be having a new repair, data from 1700 women might be available, giving 850 per arm and sufficient power to detect clinically meaningful differences. However, only about two-thirds of these were trials of synthetic mesh and it is unlikely that enough triallists would be able to provide comparable data from sufficient women, given the wide variation in the methods and types of outcome reporting and how 'secondary' prolapse surgery has been defined in the past.

Other prolapse research

New research is required into the reasons for the poor outcomes of surgery, which may suggest specific ways to improve practice. These might include:

- differences in surgical technique (which has been shown to vary considerably within PROSPECT)
- training of surgeons in the most effective surgical techniques
- better definition of the defects resulting in prolapse, including training in examination techniques, such as the POP-Q
- better selection of women who may or may not respond well to prolapse surgery (e.g. risk factors such as younger age, obstetric history)
- timing of that surgery in relation to the natural history of the progression of prolapse symptoms
- the effect of prolapse surgery on concomitant symptoms of pelvic floor dysfunction, such as bladder, bowel and sexual function
- aspects of postoperative management that may affect success, such as the need for vaginal packing
- the need to treat prolapse in more than one compartment
- the value of and need for concomitant continence surgery
- the value of preoperative and postoperative PFMT
- the value of preoperative and postoperative oestrogen treatment in postmenopausal women, and
- whether or not women who appear to have a genetic predisposition to prolapse have a higher rate of surgical failure, and whether or not this can be modified.

In addition, research is required into means of prevention of prolapse or slowing down prolapse progression. The identification of remediable causes of prolapse, or identification of factors related to poorer outcomes (such as obesity) may suggest alternative or concomitant treatments to help women.

Research should use validated and standardised terminology, and classification of conditions. In particular, it should use outcome measures that focus on the needs of women by addressing their perception of prolapse symptoms, the effect on their QoL and avoidance of adverse effects, rather than anatomical (objective) cure.

One important outcome is pain, but effective outcome measures for pain need to be developed. Ideally, the issue of chronic pain should now be addressed prospectively using standard definitions and allowing assessment of the degree of pain, as has also been noted in the context of hernia surgery.[65]

Any further research undertaken should include (where feasible and sensible to do so) comprehensive evaluation of the cost (to both the NHS and to women themselves) and QoL implications of treatment strategies on the UK NHS. When RCTs are undertaken to address questions of clinical importance, these should be accompanied by full and comprehensive economic evaluation studies. Such studies should, ideally, and where data allow, include decision-analytic modelling to explore long-term implications of treatment decisions.

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Publications

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Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Appendix 1 Information for participants and gynaecologists

Study flyer

THANK YOU
for reading this

You have been given this information by:

(name)

on

(date)

If you have any queries at the moment, please contact a member of the research team at the University of Aberdeen, telephone: [redacted] or email: [redacted].

Alternatively, you may contact your own gynaecologist.

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

STUDY FLYER

Short summary for women having prolapse surgery

Version 4: 01 March 2011

What is PROSPECT?

PROSPECT is a clinical research study that is being run in your hospital in association with researchers throughout the UK. PROSPECT is funded by the NHS Health Technology Assessment Programme and is centrally co-ordinated at the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, University of Aberdeen.

Why have I been invited to take part in PROSPECT?

You have been invited because you will be having surgery for your prolapse in the near future. We want to give you some brief information about the study now, to give you plenty time to think about it before your operation.

What is the purpose of the study?

There are several different types of prolapse operations currently being used in the NHS, some of which include the use of mesh materials.

However we do not know which type of operation is best and whether using mesh improves prolapse symptoms without causing any extra problems.

If your gynaecologist thinks that any of the types of surgery are equally suitable for you, and you agree, you will be randomly allocated (by chance) to one particular type of operation.

If you decide you do not wish to be randomised, or your gynaecologist advises a particular type of operation would be best for you, you can still be part of the study. All women in the study, whether randomised or not, will complete the same questionnaires.

If I participate in the study how will I be followed up?

If you consent to take part in PROSPECT, you would not have to undergo any tests or procedures that are not part of NHS routine care for prolapse. Everyone in the study will be followed up in exactly the same way for two years initially but also hopefully in the longer-term as it is important to find out how you are quite some time after your prolapse operation.

You would return for a clinic appointment approximately 12 months after you have had your operation (randomised women only).

Also, we would send questionnaires to you at home for you to complete at 6, 12, 18 and 24 months after you joined the study. If you take part in the study and later change your mind, you can withdraw without giving a reason.

What will happen to the results of the study?

The results of the study will be used to advise on what type of prolapse surgery should be used to treat women in the future.

What happens next?

We will send you some more detailed information around the same time as you receive your hospital admission documents. You will then have a chance to speak to your gynaecologist and a member of the study team, who will be able to answer any queries you have.

Clinic poster

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

The PROSPECT Study is investigating which prolapse operations are the safest and most effective for women with pelvic organ prolapse

If you are having prolapse surgery you may be able to take part

For further information please talk to your gynaecologist and/or the PROSPECT Recruitment Officer:

XXXXXXX

Email [redacted]

The PROSPECT website is: https://www.charttrials.abdn.ac.uk/prospect/

The PROSPECT trial is funded by the NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment (NETSCC HTA) Programme. The Chief Investigator is Prof C Glazener and the Trial Office is based within CHaRT (Centre for Healthcare Randomised Trials) in the Health Services Research Unit, University of Aberdeen.

ISRCTN:60695184 Version 1: 20 April 2009

You can also contact the study team who are organising the research:

Suzanne Breeman (Study Manager)
PROSPECT STUDY OFFICE
Tel. [redacted]

or the Chief Investigator
Prof Cathryn Glazener
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD

Tel. [redacted]

Thank you for reading this and considering taking part in this study.

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

PATIENT INFORMATION LEAFLET

The purpose of the PROSPECT research study is to compare the results of different types of surgery for women with vaginal wall prolapse, in order to identify the most effective and efficient operation.

Please take time to read this information leaflet and discuss it with your family, friends or GP if you wish.

Do not hesitate to contact us if there is anything you do not understand or if you would like more information.

Version 3: 01 April 2010

DOI: 10.3310/hta20950

1. Description of Study

There are many different operations for prolapse, depending on the type of prolapse women have and whether it is the first or a subsequent prolapse operation. Types of prolapse include the front wall of the vagina [an anterior prolapse] and/or a prolapse to the back wall [a posterior prolapse]. There is not enough evidence from previous research to let us know which operations should be used.

2. Why have I been invited to take part?

You are being invited to take part in the PROSPECT study because you will be having an operation for your vaginal prolapse. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

3. Background

One in ten women will need an operation for prolapse. All the types of prolapse surgery that you might undergo in this study are in common use in the NHS.

There are several different prolapse operations currently being used successfully in the NHS, some of which include the use of mesh or graft materials. Mesh is thought to provide extra support for the prolapse while it is healing, thus possibly reducing the chance of failure. On this basis, some doctors are already using mesh in their prolapse surgery. We do not know, however, whether there are more complications with mesh compared with operations without mesh. We need to be able to evaluate these different operations, particularly in the long term, and your participation in the study will help us do so.

If you became unable or unwilling to continue in PROSPECT, we would withdraw you from the study. We would retain, confidentially, the relevant information that we had already collected about you for the purposes of the study only.

10. Who is doing this study?

This study is being funded by the NHS National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment programme (NETSCC HTA). The research is being carried out by a group of experienced doctors and researchers from the Health Services Research Unit at the University of Aberdeen in collaboration with the British Society of Urogynaecologists, which is part of the Royal College of Obstetricians and Gynaecologists.

11. Who has approved this study?

Committee Two of the North of Scotland Research Ethics Service, your local hospital and your gynaecological consultant have given approval for this study to be carried out. An independent Steering Committee and a Data Monitoring Committee will monitor safety and ensure that the study is conducted in accordance with good research practice.

12. How do I get in touch with the research team if I want any further information about the study?

If you have any questions about the study, or any aspect of your treatment or health, please speak to your PROSPECT recruitment officer or your own gynaecology consultant or GP. Alternatively you can contact the PROSPECT Study Office (details overleaf).

DOI: 10.3310/hta20950

8. How will the information I provide be used?

We hope that over 4000 women will take part in this study during the next three years in centres across the UK. Gynaecologists will be informed of the recommendations from the study, so that in future all women can receive the best and safest operations. The results of the study will be published in scientific journals and a short version will also be available to those women who took part in the study if they wish. Women will not be identifiable in any of the study reports.

9. What if there is a problem?

We do not expect any harm to come to you by taking part in this study. All the materials and techniques are already being used in the NHS for prolapse surgery. Your participation in the study is therefore only to help us evaluate these procedures and should not involve any additional risk to you.

If you have a concern about any aspect of the study, you should ask to speak with the research team who will do their best to answer your questions (phone [redacted]). If you are still concerned and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Taking part in this study does not affect your normal legal rights. Whether or not you do take part, you will retain the same legal rights as any other patient in the NHS (which include professional indemnity insurance for negligence). If you wish to complain about your health care or any aspects of this study, the normal NHS mechanisms will be available to you. Although we do not expect participation to affect private medical insurance, please check with your insurers before agreeing to take part in the study.

You will not have to undergo any tests or procedures that are not part of routine care for prolapse.

There may be no direct benefit to you if you do take part, but you will be helping with important research enabling doctors to assess which operation is best and safest.

4. What is the purpose of the study?

The aim of the study is to answer two main questions: (1) which of the operations gives the best results and is safest, and (2) whether or not the use of mesh improves women's prolapse symptoms without causing extra problems. Therefore, once we have the results of PROSPECT, doctors in the future should be able to choose the prolapse surgery that has the best results with the fewest problems. This will mean fewer repeat operations, better health and quality of life for women, and better use of NHS facilities.

5. Do I have to take part?

It is up to you whether you decide to take part. If you do take part you would be free to withdraw at any time without giving any reason. This will not affect your current or future medical treatment. Before you decide, your gynaecologist or the PROSPECT Recruitment Officer will provide you with more information and will be happy to discuss any questions you may have. If you agree to take part, you will be asked to sign a consent form for this research study. Your gynaecologist will make you aware of all relevant issues surrounding the surgery itself, and you will sign a separate NHS information and consent form for your operation.

6. What will participation in the study involve?

As described above, there are different types of operations that you could have. If your gynaecologist thinks that all of the operations would be equally suitable for you, with your agreement you will be allocated at random to one particular type of operation. Therefore you would be put into one group by chance (randomly) and all of the women in that group will be given the same operation.

If you decide that you do not wish to be randomised, or your gynaecologist decides that a particular operation is best for you, you will be allocated to that group (type of surgery). You will still be part of the study. Your gynaecologist will discuss all of this with you.

The following diagram shows you what you will be asked to do:

Before your operation

- You will be asked to complete a booklet of questions about the problems caused by your prolapse and how this affects your life
- As part of your routine care you will have a vaginal examination to find out what type of prolapse you have and to measure its size

⇩

After your operation

- At 6, 12 and 24 months you will be sent a questionnaire to fill in and return to the PROSPECT team

⇩

Randomly allocated women only

- At 12 months you will be examined in gynaecology outpatients to check your operation was successful
- At 18 months you will be sent an extra questionnaire to fill in and return to the PROSPECT team

Each questionnaire will take about 10-20 minutes of your time to complete. It is very important that you return these booklets. Your answers will help us measure how things have changed after the operation. Although we would like you to complete the questionnaires fully, you are not obliged to answer every question if you don't want to.

With your permission, we would like to contact you again in the future to check on a) your long term health, for example by sending you other questionnaires to add information to what we already know about you, and b) to ask you to take part in other relevant studies. However, you will not have to reply to any questionnaires or take part in other studies unless you want to at that time.

7. Will the information I provide be kept confidential?

Yes, all information collected for the study at any time, will be stored using a Study Identity Number for confidentiality and will be kept secure using passwords. This includes the questionnaires that may be sent to you in the longer term as mentioned above. The information will only be available to the research team and the NHS or University bodies responsible for maintaining research standards. Your own doctor (GP) will be informed of your participation in the study.

In order to increase the usefulness of the whole study, we will confidentially link your answers with electronic data from your medical NHS records related to your health after prolapse surgery. We will ask you for specific consent to this. Again this information will be kept secure and confidential.

Surgical information sheet

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

Surgical Information Sheet for Women having Prolapse Surgery

Generic Information and Consent form for all women having prolapse surgery

1. Proposed operation:

Prolapse or Pelvic Floor Repair ☐

Hysterectomy (full or partial) ☐

Urinary Incontinence operation ☐

2. Why am I having this operation?

You and your gynaecologist have agreed that you need a prolapse operation to cure or improve your prolapse symptoms, such as a feeling of a bulge in or coming down from your vagina, a dragging or heavy sensation or problems with your urine control, bowel function or intercourse.

You should be aware that you are advised not to have any more children after the operation as another pregnancy may cause the prolapse to come back. If you have a hysterectomy (removal of the womb) as well, you will not, of course, be able to have children afterwards.

3. What will the operation involve?

Prolapse surgery can include replacing the bladder, bowel or uterus in their correct positions, or removing the uterus (hysterectomy) completely or partially, followed by repair of the weak vaginal walls. This can be done using stitches, mesh or graft materials. If mesh or graft materials are used, these can be put in place through an incision in the vaginal wall skin (known as an inlay), or using an 'introducer' (known as a 'mesh kit'). Mesh materials include man-made (plastic) materials, some of which dissolve over time while others never dissolve. Graft materials are made of natural fibres which may come from animals, humans or plants, and eventually dissolve. Your gynaecologist will discuss the exact sort available for you if necessary.

Prolapse operations can be done from below through your vagina or through your abdomen or by using a laparoscope (keyhole surgery). Even if the surgery is done through the vagina, this is still a major operation and you should be just as careful as after an abdominal operation. For example, you should not do any lifting or strenuous exercise for at least 3 months.

Version 2: 01 January 2010

You and your gynaecologist will decide the exact type of operation that you need. You should be aware, however, that whatever is planned before the operation may need to be altered when you are examined under anaesthetic in theatre. Sometimes it becomes clear that it is necessary to perform a different prolapse procedure for clinical reasons.

After your operation, your gynaecologist may place a catheter in your bladder (from below or via your abdomen) to help you pass urine at first. Your gynaecologist may also use a vaginal pack for the first day after surgery. You may also be advised to use vaginal oestrogen cream or tablets for a few weeks after surgery.

4. What type of anaesthesia will I have?

A general anaesthetic (being asleep) or a spinal anaesthetic (or epidural) to numb the lower half of your body can be used. The pros and cons of these forms of anaesthetic will be discussed with you by your gynaecologist and your anaesthetist. You will be able to choose which type of anaesthetic you would prefer, provided this is appropriate for your operation.

5. What extra operations may be carried out at the same time?

If you have stress urinary incontinence, your gynaecologist may recommend having a bladder support procedure such as placing a sling under the urethra or a colposuspension. If your womb is prolapsed, or if you have other problems such as heavy periods, your gynaecologist may recommend removing the womb completely (hysterectomy) or only the lower half of the womb (the cervix) or the upper half of the womb (subtotal hysterectomy).

Any such extra operations will of course be discussed and agreed with you beforehand.

6. What extra procedures may become necessary during the operation?

All operations carry a risk of complications such as bleeding, damage to other organs, or infection.

If there is a high blood loss, you may require a blood transfusion. Around 1 in 50 women who have a vaginal hysterectomy will need a blood transfusion, but it is less likely for other types of prolapse surgery.

If blood vessels, bladder or bowel are damaged, these will need to be repaired during the operation. This sometimes means having an abdominal operation (laparotomy) to correct the problem, prevent serious harm to your future health or save your life.

It must be stressed, however, that such events are rare and unlikely to happen.

7. What adverse effects or problems may occur after the operation?

Some problems occur frequently but are **not serious**, are to be expected in some women, and can be easily treated. These include:

- Urinary retention (being unable to pass urine after operation)
- Vaginal bleeding or discharge
- Infections e.g. in the vagina or abdomen.
- Urinary tract infection or passing urine more frequently than normal
- Pain in the abdomen, back or vagina.
- Mesh erosion through the vaginal walls (this may cause some discharge or bleeding as well as pain with intercourse).

Some more serious problems can occur after surgery, are treated as and when they arise, and include:

- Damage to blood vessels or excessive bleeding requiring return to theatre or blood transfusion
- Damage to bladder or urinary tract
- Damage to bowel
- Blood clots in the legs or lungs (venous thrombosis and embolism)
- Serious infections or pelvic abscess

8. What may I expect in the long term?

Your prolapse surgery is designed to cure your prolapse symptoms, including urine, bowel or sexual problems. However, 1 in 3 women will need another prolapse operation at some time in the future (the average time is 12 years later). Some women may also develop leakage of urine for which they will need another operation.

Your symptoms of prolapse may come back at a lesser level which may not need another operation. You may, however, have:

- Long term effects on your bladder function such as leakage of urine, having to pass urine frequently or urgently, or being unable to pass urine and needing to use a catheter long term
- Bowel symptoms such as leakage, having to rush urgently or constipation
- Difficulty or pain with intercourse, vaginal scarring or narrowing
- Buttock pain
- The need to remove mesh or graft materials
- Menopausal symptoms

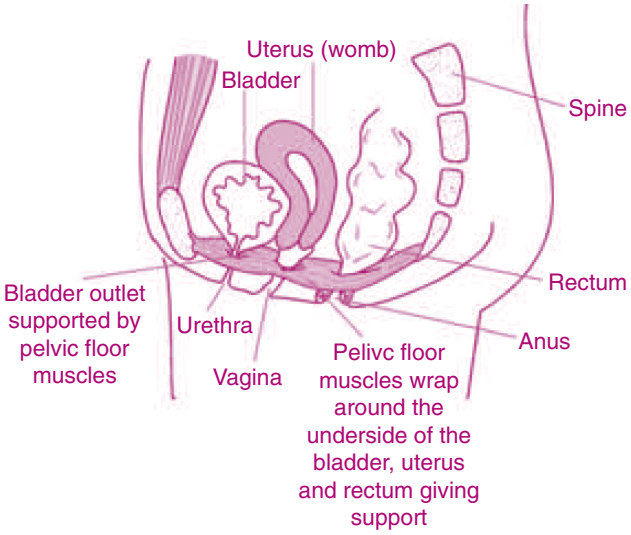
In general terms, it is not possible to predict how much you personally will benefit from surgery or whether you will develop any new problems or need further treatment for them.

9. What other prolapse treatments are available?

Women with prolapse may also practise pelvic floor muscle exercises, use oestrogen cream, or use a ring or other type of plastic pessary. These treatments may also be used after prolapse surgery for women who still have symptoms.

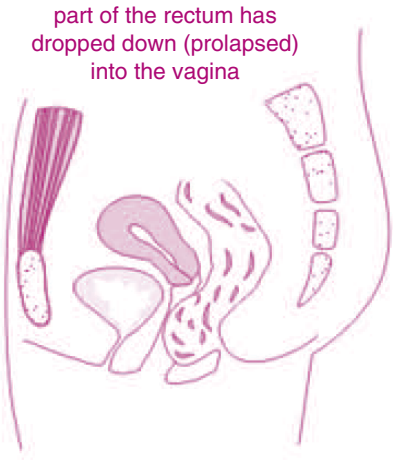
Pictures of Pelvic Organ Prolapses

1. Normal pelvic organs



2. Anterior vaginal wall prolapse (cystocele)

3. Posterior vaginal wall prolapse (rectocele)



4. Uterine prolapse

Instructions to gynaecologists

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

Instructions for gynaecologists when putting women on the waiting list for prolapse surgery

1 Explain proposed surgery, using the Prospect Surgical Information sheet. Mention uncertainty about best method of performing surgery, that mesh may be used and that this may be decided at random.

2 Mention research into prolapse surgery (PROSPECT). All women (whether randomised or not) will be involved in the study. Sign and give woman the PROSPECT Flyer.

3 Complete sticker and attach to POP-Q examination sheet.

4 **What happens next?**
The woman will receive more information about PROSPECT from a Recruitment Officer or her gynaecologist before her surgery

5 **In the letter** putting her on the waiting list please mention:

- PROSPECT and randomisation has been discussed
- If the woman is definitely **not** suitable for randomisation please specify why not
- Describe exactly what previous prolapse surgery has been carried out (ie which compartment(s), use of mesh and route of hysterectomy)
- Please specify all the compartments which need to be repaired on this occasion and ensure POP-Q is completed
- If the woman needs a continence operation please mention and refer for cystometry if necessary

Any queries please contact:
Local Researcher:
Trial Manager: Suzanne Breeman, [redacted]
Version 1: 01 January 2010

Ineligible or declined form

PROSPECT INELIGIBLE OR DECLINED FORM

Outline data on patients who are ineligible or who decline participation

Study number ☐☐☐☐☐

Q1 **Date of attempted recruitment** D D / M M / Y Y Y Y

Q2 **Year of Birth** Y Y Y Y

Q3 **Diagnosis**

Primary repair? ☐
Secondary repair? ☐
Not Known? ☐

Q4 **Operation planned** (tick all that apply)

Anterior? ☐
Posterior? ☐
Middle Compartment? ☐
Not Known? ☐

Q5 **Reasons for non-inclusion - tick all that apply**

Missed ☐
No prolapse ☐
Operation cancelled – unfit for operation ☐
Unable to give informed consent ☐ (please go to Q7)
Unable to complete study questionnaires ☐ (please go to Q7)
Patient does not want to participate in the study ☐
Other ☐

Q6 **If other, please state:**

Q7 **If unable to give informed consent or complete study questionnaires due to language problems, please state the language spoken by the participant:**

Signature: _____

Print Name: _____

ISRCTN 60695184 Version 2: 10 November 2009

Consent form

PROSPECT Prolapse Surgery: Pragmatic Evaluation and Randomised Controlled Trials

STUDY CONSENT FORM
PROSPECT: Prolapse Surgery

Participant Study No ☐☐☐☐☐

By signing this form and ticking each box I agree that I have:

Please tick ALL boxes ↓

- been given the Information Sheet about the study (Version _ Dated _ _ / _ _ / _ _) ☐
- had the opportunity to discuss the study
- received satisfactory answers to questions
- been given enough information about the study

I understand that:

- my participation is voluntary and taking part in the study may not benefit my own health
- I am free to withdraw from the study at any time without having to give a reason
- if I withdraw, this will not affect my medical care or legal rights
- I may be contacted in the future for long term follow up ☐

I agree that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Aberdeen, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. Information relevant to the PROSPECT study may be collected from my hospital and NHS records, including Office of National Statistics (ONS) and NHS central registers. ☐

I am willing to be asked in the future if I would be willing to take part in other relevant research ☐

I agree that relevant data and my contact details will be held confidentially and securely by the study office in Aberdeen, and may be subject to audit and monitoring by regulatory authorities, without breaching data confidentiality ☐

I agree that my family doctor (GP), my hospital consultant and the person I have nominated as my best contact may be told that I am taking part in this study ☐

I agree to take part in the PROSPECT study ☐

Your signature (participant) _____

Your name in block capitals _____

Date _____

For office use only

I confirm that I have explained to the person named above, the nature and purpose of the PROSPECT study and the procedures involved.

Signature _____

Date _____

CONSENT TO RANDOMISATION

I confirm that I have discussed the types of surgery suitable for me with my gynaecologist, and I agree to being **randomly allocated** to one of them. ☐

Signature of Participant _____

Date _____

I confirm that I have discussed with my patient the types of surgery suitable for her, and I agree that she can be **randomly allocated** to one of them. ☐

Signature of Gynaecologist _____

Date _____

ISRCTN60695184 Version 2: 01.01.10

Appendix 2 Participant and general practitioner letters

Baseline invitation letter

<< Date >>

Dear <<Title>> <<Surname>> Prospect STUDY No. <<……>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

You are being invited to take part in a research study because you will be having surgery for your prolapse in the near future. We want to give you some information about the study now, to give you plenty time to think about it before your operation. So we have enclosed a Participant Information Sheet and a Baseline Questionnaire.

Thank you for taking the trouble to read this information. We hope that it will be helpful in enabling you to decide whether or not you would like to participate in the PROSPECT Study. You will be approached about this when you go to hospital.

If after reading this information you think you would like to take part in this study, please complete the baseline questionnaire and bring it along with you to hospital when you come in for your pre-assessment or your operation.

Please feel free to discuss this with your family, friends or GP if you wish. Your own gynaecologist or staff at the PROSPECT Study Office will also be happy to answer any questions.

With our very best wishes and thanks for your kind help,

Yours sincerely

[Local Gynaecologist]

Enclosures Participant Information Sheet
Baseline Questionnaire

Version 2 10 November 09

General practitioner letter

<< DATE >>

Dr GPFName GPSName
GPAddress1
GPAddress2
GPAddress3
GPAddress4
GPPostCode

Patient Study Number:

Dear Dr

PROSPECT: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials.

RE: Title FName SName DOB Address1 Address2 Address3 Address4 PostCode

A multicentre UK-wide research study, funded by the NHS National Institute for Health Research Health Technology Assessment Programme is investigating which prolapse operations are the safest and most clinical and cost-effective for women with anterior and/or posterior vaginal wall prolapse. CentreHosp is one of the participating sites. The trial is needed because there is uncertainty about which type of surgery is most effective for these women.

All women who consent will be followed-up and those who are eligible will be randomised to a particular type of surgery, depending on whether they are having their first operation or have had previous prolapse surgery. Both women who have had previous prolapse surgery and those having their first operation will be included. We are following up the women after their operations initially for two years, but hopefully long-term. More detailed information about the study is provided overleaf.

Your patient has agreed to join the study. She will either be followed up as part of the non-randomised cohort or may have been randomised to one of the surgery groups as appropriate for her. Her gynaecology consultant is ConsFName ConsSName.

We will carry out postal follow-up (from Aberdeen) by asking participants to complete questionnaires after surgery and at 6, 12 and 24 months later. The questionnaires ask about general health and use of the health service as well as specific information about prolapse symptoms. She will also be reviewed in outpatients by an appropriately qualified member of the research team or a gynaecologist 12 months following her surgery.

We should not normally need to obtain any information from you. However, we would be grateful if you could contact telephone number [redacted] your patient changes address, is too ill to continue taking part, has an adverse effect from prolapse surgery or dies.

If you would like to discuss any aspect of our trial, or require any further details, please do not hesitate to contact the PROSPECT Study Office on [redacted].

Yours sincerely

Dr Suzanne Breeman
PROSPECT Trial Manager

Prof Cathryn Glazener
PROSPECT Chief Investigator

ISRCTN: 60695184

Version 1: 01 January 2010

~ PROSPECT GP INFORMATION SHEET

Title of project

Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse

Background

Around one in ten women will need prolapse surgery at some point in their lives. It is most common in women who have had children, although there has been surprisingly little research into its causes and treatment. A Cochrane review[1] and a NICE Interventional Procedures review[2] have identified that there is insufficient evidence to evaluate the effectiveness, cost-effectiveness and effect on quality of life of the different types of prolapse surgery, including whether mesh should be used.

There are numerous different operations for prolapse, depending on the type of prolapse, whether the woman is having her first or a secondary repair and the preference of the gynaecological surgeon. To date, there is a high failure rate after surgery: three in ten women who have an operation will have further surgery. This study will address anterior vaginal wall prolapse (cystocele, urethrocele) and posterior vaginal wall prolapse (rectocele, enterocele). Some women may need a concomitant procedure if there is uterine or vault prolapse (eg vaginal hysterectomy), or if she is incontinent (eg TVT).

Brief outline of the study

While the women are in hospital, they will have a routine physical examination before surgery and they will complete questionnaires both before and after their operation. Further symptom questionnaires will completed 6, 12 and 24 months later. The women will be examined and reviewed in outpatients at 12 months after surgery. Our main interest is in the cure or improvement of prolapse symptoms, as reported by the women themselves.

Ethical approval has been obtained for this study. The procedures used in the study will be standardised and agreed with a team of experienced gynaecologists from the British Society of Urogynaecology (RCOG).

The Researchers

The trial is being co-ordinated by the Centre for Healthcare Randomised Trials (CHaRT, a fully registered UK CRN clinical trials unit), at the Health Services Research Unit, University of Aberdeen. Gynaecologists in your local hospital have agreed to allow their patients who are having prolapse surgery to be invited to enter the study. All gynaecologists involved in this study will be experienced in each type of surgery to which their patients may be randomised.

If you have any questions about this study or the inclusion of your patient in it, please contact the PROSPECT Study Office in Aberdeen on [redacted].

References

1. C. Maher, K. Baessler, C. M. A. Glazener, E. Adams, and S. Hagen. Surgical management of pelvic organ prolapse in women (Cochrane Review). In: *The Cochrane Database of Systematic Reviews, Issue 3*,Anonymous Chichester, UK: John Wiley & Sons, Ltd., 2007,

2. X. Jia, C. M. A. Glazener, G. Mowatt, G. MacLennan, C. Fraser, and J. Burr. Systematic review of the efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: *http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11363*, 2008. 200 pages.

Six-month letter

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study.

We have enclosed your 6 month review questionnaire. We are keen to find out how you have been getting on during the last six months since your prolapse surgery.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the Prospect Study and for completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures Six month Prospect questionnaire
Reply-paid envelope

Version 2 June 2009

Six-month reminder letter 1

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study to date.

We sent you the enclosed 6 month review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last six months since your prolapse surgery. Unfortunately we have not yet received your answers.

We appreciate how busy you must be, but believe this to be an important study for women's health. Your reply is very important to us. If your reply is already in the post, I would like to thank you for your help and apologise for this reminder.

We are therefore enclosing another copy, and would be most grateful if you could take a few minutes of your time to complete it, and return it in the envelope provided (no stamp required). Please note that ALL the information you give will be treated with the strictest confidence.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

We would like to thank you very much for taking part in the Prospect Study and in completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures 6-month Prospect questionnaire
Reply-paid envelope.

Version 2 June 2009

Six-month reminder letter 2

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study to date.

We sent you a 6 month review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last six months since your prolapse surgery. Unfortunately we have not yet received your answers.

We appreciate how busy you must be, but your answers to the questionnaire are very important to us. If you cannot answer all the questions don't worry. Please send it to us when you have answered as much as you can, using the envelope provided (no stamp required).

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study on [redacted]. Please note that ALL the information you give will be treated with the strictest confidence. If your reply is already in the post, I would like to thank you for your help and apologise for this reminder.

We would like to thank you very much for taking part in the Prospect Study and in completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures 6 month Prospect questionnaire
Reply-paid envelope

Version 1 April 09

One-year letter

<< Date >>

<<Title>> <<Name>> << Surname>> PROSPECT STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY : PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study – you very kindly agreed to help this research project when you had your prolapse surgery.

We are keen to find out how you have been getting on during the last year since your operation. We have enclosed a review questionnaire, and would be very grateful if you could fill it in.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures One year PROSPECT questionnaire
Reply-paid envelope.

Version 2 June 2009

One-year reminder letter 1

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study.

We sent you a one year review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last year since your prolapse surgery. Unfortunately we have not yet received your reply.

We appreciate how busy you must be, but we believe this to be an important study for women's health. Your reply is very important to us.

We are therefore enclosing a second copy of the questionnaire, and would be most grateful if you could give us a little of your time to complete it, and return it in the envelope provided (no stamp required). Please note that ALL the information you give will be treated with the strictest confidence. If your reply is already in the post, we would like to thank you for your help and apologise for this reminder.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire. Your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures 1 year PROSPECT questionnaire
Reply-paid envelope.

Version 2 June 2009

One-year reminder letter 2

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY : PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study to date.

We sent you a one year review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last year since your prolapse surgery. Unfortunately we have not yet received your answers.

We appreciate how busy you must be, but your answers to the questionnaire are very important to us. If you cannot answer all the questions don't worry. Please send it to us when you have answered as much as you can, using the envelope provided (no stamp required). If your reply is already in the post, we would like to thank you for your help and apologise for this reminder.

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please note that ALL the information you give will be treated with the strictest confidence.

We would like to thank you very much for taking part in the PROSPECT Study and in completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager
Enclosures One year Prospect questionnaire
Reply-paid envelope

Version 1 April 09

One-year additional letter

<< Date >>

<<Title>> <<Name>> << Surname>> PROSPECT STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study – you very kindly agreed to help this research project when you had your prolapse surgery.

Thank you for returning your one year questionnaire. Would you be kind enough to give us some additional information about your current bladder and bowel function? We would be very grateful if you could fill it this additional questionnaire.

Although some of the questions may not seem relevant we would like you to complete the questionnaire as fully as you can. However, you are not obliged to answer any question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire. Your views about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures One year additional PROSPECT questionnaire
Reply-paid envelope.

Version 1 10 November 2009

One-year addition reminder letter

<< Date >>

<<Title>> <<Name>> << Surname>> PROSPECT STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study – you very kindly agreed to help this research project when you had your prolapse surgery.

We would be very grateful if you could complete both of the questionnaires enclosed. Although some of the questions may not seem relevant we would like you to complete the questionnaire as fully as you can. However, you are not obliged to answer any question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire. Your views about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures One year PROSPECT questionnaire
One year additional PROSPECT questionnaire
Reply-paid envelope.

Version 1 10 November 2009

Costs questionnaire letter

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study.

We enclose a questionnaire asking about how much it cost **you** to use the health service. We wish to know how much money and time were spent by you and any companion when you attended appointments and as a result of any hospital admission you may have had.

Although some of the questions may not seem relevant we would like you to complete the questionnaire as fully as you can. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures PROSPECT Participants Costs questionnaire
Reply-paid envelope.

PROSPECT is funded by the NIHR Health Technology Assessment Programme

Version 1, 11 November 2009

Costs questionnaire reminder letter

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study to date.

We sent you a participant cost questionnaire a few weeks ago. We are keen to find out about how much it cost **you** to use the health service. Unfortunately we have not yet received your answers.

We appreciate how busy you must be, but your answers to the questionnaire are very important to us. If you cannot answer all the questions don't worry. Please send it to us when you have answered as much as you can, using the envelope provided (no stamp required).

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study on [redacted]. Please note that ALL the information you give will be treated with the strictest confidence. If your reply is already in the post, I would like to thank you for your help and apologise for this reminder.

We would like to thank you very much for taking part in the Prospect Study and for completing the questionnaire.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures Participant Cost questionnaire
Reply-paid envelope

PROSPECT is funded by the NIHR Health Technology Assessment Programme

Version 1, 01 April 2010

Two-year letter

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY: PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the Prospect Study – you very kindly agreed to help this research project when you had your prolapse surgery.

We are keen to find out how you have been getting on during the last two years since your operation. We have enclosed a review questionnaire, and would be very grateful if you could fill it in.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please return the questionnaire in the reply-paid envelope provided (no stamp is required).

We would like to thank you very much for taking part in the Prospect Study and for completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures Two year Prospect questionnaire
Reply-paid envelope.

Version 2 June 2009

Two-year reminder letter 1

<< Date >>

<<Title>> <<Name>> << Surname>> Prospect STUDY No. <<…….>>
.<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY : PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study.

We sent you a two year review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last two years since your prolapse surgery. Unfortunately we have not yet received your reply.

We appreciate how busy you must be, but we believe this to be an important study for women's health. Your reply is very important to us.

We are therefore enclosing a second copy of the questionnaire, and would be most grateful if you could give us a little of your time to complete it, and return it in the envelope provided (no stamp required). Please note that ALL the information you give will be treated with the strictest confidence.

Although some of the questions may not seem relevant we would like you to complete the questionnaire fully. However, you are not obliged to answer every question if you do not want to. If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted]. If your reply is already in the post, we would like to thank you for your help and apologise for this reminder.

We would like to thank you very much for taking part in the PROSPECT Study and for completing the questionnaire. Your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures 2-year PROSPECT questionnaire
Reply-paid envelope.

Version 2 June 2009

Two-year reminder letter 2

<< Date >>

<<Title>> <<Name>> << Surname>> PROSPECT STUDY No
<<Address 1>>
<<Address 2>>
<<Address 3>>
<<Address 4>>
<<Postcode>>

Dear <<Title>> <<Surname>>

The PROSPECT STUDY : PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials

Thank you very much for taking part in the PROSPECT Study.

We sent you a two year review questionnaire a few weeks ago. We are keen to find out how you have been getting on during the last two years since your prolapse surgery. Unfortunately we have not yet received your answers.

We appreciate how busy you must be, but your answers to the questionnaire are very important to us. If you cannot answer all the questions don't worry. Please send it to us when you have answered as much as you can, using the envelope provided (no stamp required). If your reply is already in the post, we would like to thank you for your help and apologise for this reminder.

If you have any worries or problems in completing the questionnaire, a friend or relative may be able to help you. If still in doubt, do please contact the Prospect Study Office on [redacted].

Please note that ALL the information you give will be treated with the strictest confidence.

We would like to thank you very much for taking part in the PROSPECT Study and in completing the questionnaire as your views and information about your recovery are very important to improving the management of women having prolapse surgery in the future.

With our very best wishes and thanks for your kind help,

Yours sincerely

Trial Manager

Enclosures Two year Prospect questionnaire
Reply-paid envelope

Version 1 April 09

Best contact form

Study Number | | | | | |

Date form filled in D D M M Y Y

BEST CONTACT FORM

We would be very grateful if you could send this form back indicating:

- **Any change of address for your relative/friend *(question 1)***
- **Any issues or comments that may have prevented us from contacting your relative/friend *(question 2)***

CONFIDENTIAL

1. PLEASE GIVE DETIALS OF ANY NEW ADDRESS FOR YOUR FRIEND/RELATIVE

House Name

House Number

Street Name

District

Town/City

County

Postcode

Telephone No
(including code)

2. ANY OTHER ISSUES OR COMMENTS

Thank you very much for filling in this form. Please return it to the CHaRT Study Office, Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD in the prepaid envelope provided.

Please do not hesitate to telephone the Study Office on [redacted] if you have any queries.

First letter to best contact

Study number | | | | | |

<< Date >>

«CurrentTitle» «CurrentFName» «CurrentSName»
«CurrentAddress1»
«CurrentAddress2»
«CurrentAddress3»
«CurrentAddress4»
«CurrentPostCode»

Dear «CurrentTitle» «CurrentSName»

We are writing to you because << *participant's name*>> of << *participant's address*>> has agreed to take part in a research study that we are co-ordinating.

She has nominated you as her "best contact". We ask people taking part in studies to nominate a "best contact". A "best contact" is not the same as a person's "next of kin", and we prefer to have a "best contact" who does not live at same address, though we appreciate that this is not always possible. We only get in touch with the "best contact" when we cannot contact the participant themselves, for example if they have moved house or are in hospital.

I hope you are content to act as a "best contact" for the above person. If you are, we will keep your details securely in accordance with the data protection legislation. We will not give your details to anyone outside the study team. We will only contact you if we cannot contact the participant themselves.

If you do not wish to act as a "best contact" for the above person please, get in touch with us and we will remove your details from our database. You can do this either by:

- Returning the attached reply slip to the study office in the enclosed pre-paid envelope;
- Emailing us at [redacted] quoting both your name and the study number above;
- Telephoning us on [redacted]. If no-one is there to take your call, please leave a message quoting both your name and the study number above. It would be helpful if you could also leave your telephone number in case we need to get in touch with you.

With very many thanks for your help.

Yours sincerely

Trial Manager

«refPatientNo»

REPLY SLIP

Study number | | | | | |

I, <<insert best contact's name>> do not wish to act as a "best contact" for <<insert participants name>>.

Signed: …… Date: ……/……./…….

Best contact reminder letter

Study number | | | | | |

<< Date >>

«CurrentTitle» «CurrentFName» «CurrentSName»
«CurrentAddress1»
«CurrentAddress2»
«CurrentAddress3»
«CurrentAddress4»
«CurrentPostCode»

Dear «CurrentTitle» «CurrentSName»

We wrote to you recently and do not appear to have received a response. Please accept our apology if this has crossed in the post.

We are writing to you because << *participant's name*>> of << *participant's address*>> has agreed to take part in a research study that we are co-ordinating.

She has nominated you as her "best contact". We ask people taking part in studies to nominate a "best contact". A "best contact" is not the same as a person's "next of kin", and we prefer to have a "best contact" who does not live at same address, though we appreciate that this is not always possible. We only get in touch with the "best contact" when we cannot contact the participant themselves, for example if they have moved house or are in hospital.

I hope you are content to act as a "best contact" for the above person. If you are, we will keep your details securely in accordance with the data protection legislation. We will not give your details to anyone outside the study team. We will only contact you if we cannot contact the participant themselves.

If you do not wish to act as a "best contact" for the above person please, get in touch with us and we will remove your details from our database. You can do this either by:

- Returning the attached reply slip to the study office in the enclosed pre-paid envelope;
- Emailing us at [redacted] quoting both your name and the study number above;
- Telephoning us on [redacted]. If no-one is there to take your call, please leave a message quoting both your name and the study number above. It would be helpful if you could also leave your telephone number in case we need to get in touch with you.

With very many thanks for your help.

Yours sincerely

Trial Manager

REPLY SLIP

Study number | | | | | |

I, <<insert best contact's name>> do not wish to act as a "best contact" for <<insert participants name>>.

Signed: …… Date: ……/……./…….

Second letter to best contact

Second letter to Best Contact

Study number | | | | | |

<< Date >>

«Merge Record #»
«Merge Record #»
«Merge Record #»
«Merge Record #»
«Merge Record #»

Dear «Merge Record #»

We wrote to you previously because << *participant's name*>> of << *participant's address*>> had agreed to take part in a research study and had nominated you as her 'best contact'.

The reason why we are contacting you now is that we have been unable to contact << participant's name>>. We would therefore be very grateful if you could help us by completing the attached 'best contact form' and returning it in the envelope provided.

Please do not hesitate to get in touch with us if you have any queries in relation to this letter and/or the best contact form.

Many thanks for your help.

Yours sincerely

Trial Manager

Appendix 3 Case report forms

Log book

Study Centre No

PROSPECT Log Book

Study Number	Date for Admission	Name	Date of Birth	Baseline Q and PIS sent	Seen Y/N *	Consent Y/N *	**Baseline Q (tick)**	Randomised A B C D or NOT rand. **	Theatre Informed	RO CRF data entered

* If No, complete ineligible/declined form

** A: Standard midline repair; B: Standard repair with mesh inlay (non-absorbable/hybrid mesh); C: Standard repair with mesh inlay (biological mesh); D: Mesh kit

Version 2: 10 November 2009

Surgical assessment form

Surgical Assessment Form (SAF)

PROSPECT PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

Please measure while patient is pushing down.

Date of POP-Q D D M M Y Y **Consultants Name:**_____

If pessary is currently in use, use last recorded POP Q or go to A2.

Genital Hiatus	Perineal Body	Total Vaginal Length
cm	cm	cm

	External						Hymen			Internal							
cm	+6	+5	+4	+3	+2	+1	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
Aa																	
Ba																	
C																	
D																	
Bp																	
Ap																	
	Stage 3 or 4 (depending on tvl)					Stage 2			S1	Stage 0 or 1 (depending on TVL)							

Cervix present Yes ☐ No ☐

Bladder/empty Yes ☐ No ☐

Bowel/empty Yes ☐ No ☐

Maximum protrusion seen Yes ☐ No ☐

[Picture of POP-Q here]

A1 If ANTERIOR, what type of anterior prolapse does the woman have?

Midfascial ☐ Paravaginal ☐ Both ☐ Unknown ☐ No anterior prolapse ☐

A2 What stage of prolapse does the woman have (0 to 4 in each box)?

Anterior (a) ☐ Posterior (p) ☐

Cervix/uterus (C) ☐ OR Vault/cuff (C) ☐

A3 Which compartment is going to be repaired?

Anterior (a) ☐ Posterior (p) ☐

Cervix/uterus (C) ☐ OR Vault/cuff (C) ☐

Suitable for randomisation? YES / NO

Primary? ☐ **Secondary?** ☐

Height	Weight	BMI
cm	kg	

Please attach address label and enter contact telephone number(s) if willing to be contacted by PROSPECT researcher (by post and/or telephone)

Place label here (top and bottom copy)

Woman's contact telephone number(s)
1.

2.

Permission to leave message? YES / NO

Please return top copy to Local Recruitment Officer in envelope provided and file bottom copy in notes.

Version 2 01 November 2011

Recruitment officer case report form

PROSPECT Study ID

Recruitment Officer (RO) Information Case Report Form (CRF) (to be filled in at each site by RO or gynaecologist)

SCREENING QUESTIONS FOR RO TO ASSESS ELIGIBILITY FOR PROSPECT

What type of prolapse operations are planned for this woman?

	Yes	No	Don't Know*
Anterior repair only	☐	☐	☐
Posterior repair only	☐	☐	☐
Both anterior and posterior repair	☐	☐	☐
Vault suspension, hysterectomy or cervical amputation	☐	☐	☐
Continence operation (eg TVT, colposuspension)	☐	☐	☐

If **Yes** to Continence operation **ONLY** — **STOP HERE and complete Ineligible or Declined form**

* If planned operations are not known or pelvic floor repair type is unspecified, please check in notes, or ask the woman's consultant.

EXPLAIN STUDY AND SIGN CONSENT FORM

Not recruited to PROSPECT ☐ — **STOP HERE and complete Ineligible or Declined form**

Section A Contact information from woman and notes

A1 PATIENT DETAILS (Sticker may be used below)

Title ☐ Mrs ☐ Miss ☐ Ms ☐ Other _____

First name _____

Surname _____

Date of birth D D M M Y Y _____ _____

NHS/CHI number Record/Hospital number

Address _____ *could use hospital label*

Telephone No _____ Mobile _____

Email Address _____

A2 CONSULTANT DETAILS

Title ☐ Mr ☐ Dr ☐ Prof ☐ Ms Other _____

Initials _____ Surname _____

A3 GP DETAILS

Initials _____ Surname _____

Address _____

A4 BEST CONTACT DETAILS

Title ☐ Mr ☐ Mrs ☐ Miss ☐ Ms Other _____

First name _____

Surname _____

Address _____

Telephone No _____

A5 RELATIONSHIP OF BEST CONTACT TO PARTICIPANT

Please specify _____

Have you asked the woman to tell this person that she has given us these details? Yes ☐

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

Section B General information from woman

B1 Have you ever had any of the following operations or treatments in the past?

	Yes	No	Don't Know
A previous operation for prolapse **(See D8)**	☐	☐	☐
A vaginal hysterectomy (from below) **(See D8)**	☐	☐	☐
An abdominal hysterectomy (via your tummy) **(See D8)**	☐	☐	☐
Vaginal pessary or ring currently?	☐	☐	☐
Physiotherapy treatment for prolapse	☐	☐	☐
Physiotherapy treatment for urinary incontinence	☐	☐	☐
An operation for urinary incontinence	☐	☐	☐
Drug treatment for urinary incontinence	☐	☐	☐

B2 Please could you tell me a little about the babies you have had?

Number of deliveries ☐☐ (count twins as two separate births)

B3 Year last child born **(year)** ☐Y☐Y☐Y☐Y

B4 Types of delivery

Number of **normal vaginal** deliveries ☐
Number of **Caesareans before** labour (elective) ☐
Number of **breech** (vaginal) deliveries ☐
Number of **forceps** deliveries ☐
Number of **Caesareans during** labour (emergency) ☐
Number of **vacuum** extraction deliveries ☐

B5 Were any of these twin deliveries?

Yes ☐ No ☐ (If **Yes**) Enter number of sets of twins: ☐

Study Number ☐☐☐☐☐ Recruitment Officer CRF

Section C Baseline (pre-operative) clinical patient information from notes or examination of woman

C1 Date of POP-Q D D M M Y Y

From last recorded POP-Q, without pessary.
***If not available*, repeat before operation (if pessary currently in use, go to C3).**

	External					Hymen			Internal								
cm	+6	+5	+4	+3	+2	+1	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
Aa																	
Ba																	
C																	
D																	
Bp																	
Ap																	
	Stage 3 or 4 (depending on tvl)					Stage 2			S1		Stage 0 or 1 (depending on tvl)						

Genital Hiatus		Perineal Body		Total Vaginal Length	
	cm		cm		cm

Cervix present Yes ☐ No ☐
Bladder/empty Yes ☐ No ☐
Bowel/empty Yes ☐ No ☐
Maximum protrusion seen Yes ☐ No ☐

Height		Weight		BMI
	cm		kg	

C2 What stage of prolapse does the woman have (0 to 4 in each box)?

Anterior (a) ☐ Posterior (p) ☐
Cervix/uterus (C) ☐ OR Vault/cuff (C) ☐

C3 If ANTERIOR, what type of anterior prolapse does the woman have?

Midfascial ☐ Paravaginal ☐ Both ☐
Unknown ☐ No anterior prolapse ☐

Section D — Baseline information needed for randomisation from woman and notes

D1 PROSPECT Study consent form signed:

Yes ☐ No ☐ (If **No**, stop here and sign)

D2 Surgery-specific leaflet received by woman:

Yes ☐ No ☐ (If **No**, give Surgical Information Sheet)

D3 Centre (named, already known from Study ID no)

D4 Date of birth D D M M Y Y

D4a Age (Auto-calculated from DoB):

<60 yrs ☐ ≥60 yrs ☐

D5 Type of prolapse for planned repair

	Yes	No
Anterior	☐	☐
Posterior	☐	☐

D6 Concomitant upper vaginal prolapse surgery planned

	Yes	No
Hysterectomy (vaginal)	☐	☐
Hysterectomy (abdominal)	☐	☐
Cervical amputation	☐	☐
Vault repair *eg sacrospinous mesh suspension, sacrocolpopexy*	☐	☐

(YES to any one of these is taken as a concomitant middle compartment procedure)

(If YES to a concomitant middle compartment procedure but NO to both anterior and posterior repair, then eligible for comprehensive cohort only)

D7 Concomitant incontinence surgery planned (e.g. TVT, colposuspension)

Yes ☐ No ☐

Study Number ☐☐☐☐☐ Recruitment Officer CRF

D8 **Has the woman had a previous prolapse repair?**

Yes ☐ No ☐ If no, go to D9

What was the previous repair compartment?

D8a Anterior only: Number of repairs ☐ Mesh used: Yes ☐ No ☐

D8b Posterior only: Number of repairs ☐ Mesh used: Yes ☐ No ☐

D8c Compartment unknown ☐ *(assume that the woman is having a primary repair)*

D8d Previous hysterectomy Yes ☐ No ☐

D8e Previous cervical amputation Yes ☐ No ☐ *(if without A or P, we assume that the woman is having a primary repair)*

D8f Previous vault procedure Yes ☐ No ☐ *(if without A or P, we assume that the woman is having a primary repair)*

D9 **(calculated by database from response to D5 and D8)**

Therefore, type of prolapse surgery planned is: Primary ☐ Secondary ☐

D10 **Is woman eligible for randomisation AND is consent to randomisation signed?**

(A) BY WOMAN Yes ☐ No ☐

(B) BY GYNAECOLOGIST Yes ☐ No ☐

(If No to either, woman is eligible for Comprehensive Cohort only)

D11 **If No, reason for not randomising:**

Patient declined ☐ Reason ☐

Gynaecologist declined ☐ Reason ☐

D12 **Types of mesh available for randomisation:** **Yes**

Synthetic non-absorbable ☐

Biological ☐

Mesh kit ☐

D13 (After entry of above details to Prospect DB) **Randomised allocation is:**

Primary: **Standard midline** ☐ **Secondary:** **Standard midline** ☐

Synthetic mesh inlay ☐ **Synthetic mesh inlay** ☐

Biological mesh inlay ☐ **Mesh Kit** ☐

(or if not randomised) COMPREHENSIVE COHORT ☐

D14 **Theatre informed / arrangements made to implement allocated procedure**

Yes ☐ No ☐

Section E Intra-operative (theatre) information from notes or gynaecologist

E1 Date of admission D D M M Y Y

E2 Date of operation D D M M Y Y

E3 Grade of Operating Gynaecologist

Consultant ☐ Specialty doctor ☐

Registrar /junior ☐ Supervised by consultant Yes ☐ No ☐

E4 Grade of Anaesthetist

Consultant ☐ Specialty doctor ☐

Registrar /junior ☐ Supervised by consultant Yes ☐ No ☐

E5 Operation time

Please specify time of (*using 24 hour clock*):

Entry into anaesthetic room: H H : M M

Time of leaving operating room: H H : M M

E6 Which type of anaesthetic was used? *(Tick all relevant boxes)*

General ☐ Spinal / epidural ☐

Local ☐ Other (please give details) ☐

If Other anaesthetic, please give details:

E7 Was a prophylactic antibiotic used for the operation? Yes ☐ No ☐

E8 Type of vaginal prolapse surgery carried out:

Anterior ☐ **Type of mesh used:**

No mesh ☐

Synthetic non-absorbable inlay ☐

Biological inlay ☐

Mesh kit ☐

Posterior ☐ **Type of mesh used:**

No mesh ☐

Synthetic non-absorbable inlay ☐

Biological inlay ☐

Mesh kit ☐

E9 Did the woman receive the randomised allocation?

Yes ☐ No ☐ **Comprehensive Cohort (N/A)** ☐

(If No, go to E9a)

E9a If NO - Please give reason:

E10 Concomitant upper compartment prolapse surgery:

VAGINAL		**ABDOMINAL**	
Cervical amputation	☐	Abdominal hysterectomy	☐
Vaginal hysterectomy	☐	*Abdominal vault fixation	☐
* Vaginal vault suspension / fixation	☐	*Abdominal uterine suspension	☐
* Vaginal uterine suspension	☐		

*** E10a** If **Vault** or **Uterine Suspension** procedure, please give details of mesh used:

No mesh	☐	Biological	☐
Synthetic non-absorbable	☐	Mesh kit	☐

If any **other** prolapse surgery, enter details in **E12**

E11 Concomitant incontinence surgery:

Continence procedure (vaginal) ☐ Continence procedure (abdominal) ☐

E11a Please give details of mesh used for continence surgery:

No mesh	☐
Synthetic non-absorbable	☐
Biological	☐

E12 If any other surgery, please give details:

E13 What was the estimated blood loss? ☐☐☐☐ mls (add to E17)

E14 Was a catheter inserted in theatre? Yes ☐ No ☐ Don't know ☐

E15 If Yes, what type of catheter was used?

Suprapubi	☐	oth	☐
Urethral	☐	None	☐
		Don't know	☐

E16 Was a vaginal pack inserted in theatre? Yes ☐ No ☐ Don't know ☐

E17 Intra-or post operative complications before discharge (If none tick:) ☐

Ureteric injury	Yes ☐	No ☐	If YES, complete Adverse Events Form
Bladder injury	Yes ☐	No ☐	If YES, complete Adverse Events Form
Bowel injury	Yes ☐	No ☐	If YES, complete Adverse Events Form
Vascular injury	Yes ☐	No ☐	If YES, complete Adverse Events Form
Neurological injury	Yes ☐	No ☐	If YES, complete Adverse Events Form
Blood loss > 500 ml	Yes ☐	No ☐	If YES, complete Adverse Events Form
Peri or postoperative blood transfusion	Yes ☐	No ☐	If YES, complete Adverse Events Form
Peri or post-operative thromboembolism	Yes ☐	No ☐	If YES, complete Adverse Events Form
Death	Yes ☐	No ☐	If YES, complete Adverse Events Form

Section F Postoperative information from notes or nursing cardex

POSTOPERATIVE DATA

F1 Return to theatre for procedure related event within 72 hours Yes ☐ No ☐ Details

F2 Catheterisation required for more than 10 days post op Yes ☐ No ☐ Details

F3 Pain relief Oral Yes ☐ No ☐

Parenteral Yes ☐ No ☐

F4 Laxatives Yes ☐ No ☐

F5 Infection Yes ☐ No ☐

If **Yes**:

F5a UTI Yes ☐ No ☐

F5b Wound Infection Yes ☐ No ☐

F5c Pelvic sepsis/ abscess/ septicaemia Yes ☐ No ☐ If **Yes**, complete Adverse Events Form

F6 Treatment for infection

Antibiotics Yes ☐ No ☐

F7 Haematoma Yes ☐ No ☐

F8 Other adverse events postoperatively Yes ☐ No ☐

If YES, give details and contact study office

F9 Date of discharge D D M M Y Y

Twelve-month clinic review form

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

PROLAPSE 12 MONTH CLINIC REVIEW ASSESSMENT FORM

CONSULTANT _____ **STUDY NUMBER** _____

Date of birth of woman D D M M Y Y

Date when woman seen D D M M Y Y

PLEASE COMPLETE THE POP-Q FIRST
AND TRY TO REMAIN "BLIND" TO STUDY ALLOCATION

1 **Did you know which randomised study group this woman was in *prior to* completing the POP-Q (e.g. woman may volunteer information)?** Yes ☐ No ☐

2 **Did you know which operation this woman actually received *prior to* completing the POP-Q (e.g. woman may volunteer information)?** Yes ☐ No ☐

If this woman did not attend for her 12 month review, please try to complete this form as fully as possible from her medical records, and tick here: ☐

Signature: _____

Print Name: _____

Status
- **Consultant/ Associate Specialist** ☐
- **Junior doctor** ☐
- **Recruitment Officer** ☐

Version 4: 01 March 2011

Section A Clinical examination and POP-Q

A1 **Please mark measurements by ticking the boxes corresponding to the measurements (this will visually enable you to stage the prolapse), and enter the measurements for GH, PB and TVL.**

Please measure while woman is pushing down. **Date of POP-Q** D D M M Y Y

	External					Hymen		Internal									
cm	+6	+5	+4	+3	+2	+1	0	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
Aa																	
Ba																	
C																	
D																	
Bp																	
Ap																	
	Stage 3 or 4 (depending on tvl)					Stage 2			S1		Stage 0 or 1 (depending on tvl)						

Genital Hiatus	Perineal Body	Total Vaginal Length
_____ cm	_____ cm	_____ cm

Cervix present	Bladder empty	Bowel empty	Maximum protrusion seen
Yes / No	Yes / No	Yes / No	Yes / No

A2 **What grade of prolapse does the woman have (0 to 4 in each box)?**

Anterior (Ba) ☐ Posterior (Bp) ☐

Cervix/uterus (C) ☐ OR Vault/cuff (C) ☐

A3 **If ANTERIOR, what type of anterior prolapse does the woman have?**

Midfascial ☐ Paravaginal ☐ Both ☐ Unknown ☐ No anterior prolapse ☐

A4 **Mesh exposure/extrusion/graft problems observed on examination?**

Yes ☐ No ☐ Not applicable ☐

A5 **Other problem identified on examination?**

Yes ☐ No ☐

If yes to A4 or A5, please give details and **complete Adverse Event Form**

Serious adverse event/death report form

Serious Adverse Event/Death Report Form

To be completed for any Serious Adverse Event (SAE) that is:

- **related (resulted from administration of any of the research procedures) and**
- **expected or unexpected (expected events are listed in section 8.4.2 of the protocol)**

ALL deaths must be recorded using this Report Form

PROSPECT Study No

Report Date Day / Month / Year

		/			/				

Patient Details:

Patient's Name

Date of Birth Day / Month / Year

Hospital Number

Q1 Type of event *(cross all appropriate to adverse event – if any boxes are crossed the adverse event is "serious")*

- **Patient died**
- **Hospitalisation**
- **Prolongation of existing hospitalisation**
- **Persistent or significant disability or incapacity**
- **Life threatening**
- **Considered medically significant by the investigator**

Q2 If the Serious Adverse Event was expected, please cross all that apply

Intraoperative occurrences associated with surgery

- **Injury to organs**
- **Excess blood loss**
- **Blood transfusion**
- **Anaesthetic complications**
- **Death**

Postoperative occurrences associated with surgery

- **Thrombosis**
- **Infection (UTI, sepsis, abscess)**
- **Pain**
- **Urinary retention**
- **Bowel obstruction**

ISRCTN: 60695184 Version 4: 01 July 2013

Constipation	☐
Mesh erosion	☐
Excess blood loss	☐
Vaginal adhesions	☐
Haematoma	☐
Skin tag	☐
Granulation tissue	☐
New or persistent urinary tract symptoms	☐
Death	☐

Q3 Date of event

Day Month Year

☐☐ / ☐☐ / ☐☐☐☐

Q4 Location

Q5 Describe the circumstances of the event

Q6 Details of any intervention required

Assessment of whether the event was caused by trial participation:

Q7 Is it reasonably likely that the adverse event was caused by taking part in PROSPECT?

Yes ☐ No ☐

Q7a Why?

Q8 If event likely to have been caused by taking part in PROSPECT, describe any implications for the safety of study participants and how will these be addressed?

Q9a Name and position of person making this judgment

Q9b Date of assessment

Day Month Year

☐☐ / ☐☐ / ☐☐☐☐

Withdrawal/change of status form

WITHDRAWAL/ CHANGE OF STATUS

To be completed on withdrawal/change of status from study

Study No | | | | | |

Q1 Date of withdrawal Day | | / Month | | / Year | | | |

Reason for withdrawal

Q2 Participant decided to withdraw? (state reason)

Q3 Any medical reason for withdrawal? (please state reason)

What is participant withdrawing from?

Q4 Randomisation?

Yes ☐ No ☐

Q5 Follow-up clinic visits?

Yes ☐ No ☐

Q6 Completing questionnaires?

Yes ☐ No ☐

Q7 Relevant outcome data being collected (via hospital and GP records)?

Yes ☐ No ☐

Surgical standardisation form

Standardisation of Surgical Procedures in PROSPECT

Please complete last column to indicate your own practice when performing prolapse surgery (circle or amend). If you vary your technique, please tell us about the one you use most often.

Name……..

Centre……..

1. Standard anterior repair

Date: **……/……/20…..**	**Procedures**	**Local practice (variations)** ***Please circle or amend***
	Midline skin incision through fascial layer and dissection of bladder off cervix / vault	Midline incision Other (details)…….. ……
	+/- hydrodissection with 1 in 200,000 adrenaline	Yes No Volume: ……..ml
Anterior Repair Type 1	Dissect fascia off vaginal epithelium	Blunt dissection? Sharp dissection?
Anterior Repair Type 2	Leave fascia on vaginal skin Dissection laterally (but not all the way to the 'white line') and sutures placed into fascia in this area	Blunt dissection? Sharp dissection?
Closure	Fascia and skin closed separately (2-layer closure) Plicate fascia in midline if midline defect? Yes No Separate closure of other fascial defects? Yes No Paravaginal repair? Yes No Skin closed	**FASCIA** PDS or Vicryl? Fascial sutures: • continuous locking • continuous non-locking • interrupted? **SKIN** PDS or Vicryl? Skin sutures: • continuous locking • continuous non-locking • interrupted?

Version 7, 01 August 2011

2. Standard Posterior repair

Date: **……/……/20…..**	**Procedures**	**Local practice (variations)** ***Please circle or amend***
	Midline skin incision through fascial layer	Midline incision Other (details)…….. ……
	+/- hydrodissection with 1 in 200,000 adrenaline	Yes No Volume: ……..ml
Posterior Repair Type 1	Dissect fascia off vaginal epithelium	Blunt dissection? Sharp dissection?
Posterior Repair Type 2	Leave fascia on vaginal skin Dissection laterally (but not all the way to the sacrospinous ligament) and sutures placed into fascia in this area	Blunt dissection? Sharp dissection?
Rectal plication	Optional	Yes No
Closure	Fascia and skin closed separately (2-layer closure) Plicate fascia over rectum in midline if midline defect? Yes No Separate closure of other fascial defects? Yes No Skin closed	**FASCIA** PDS or Vicryl? Fascial sutures: • continuous locking • continuous non-locking • interrupted? **SKIN** PDS or Vicryl? Skin sutures: • continuous locking • continuous non-locking • interrupted?
Levator plication in midline	**NOT** to be done as causes dyspareunia	
Rectal examination	PR examination during dissection or after operation to ensure sutures do not penetrate rectal wall	Yes No

3. Mesh / graft inlay

Date: **……/……/20…..**	**Procedures**	**Local practice (variations)** ***Please circle or amend***
	Nonabsorbable mesh Biological graft Mesh Kit	Type: …… Type: …… Type: ……
	How many kit procedures have you performed?	<10; 10-20; 20-49; > 50
Lateral dissection of pubocervical fascia from vaginal wall	Separate bladder / rectum from fascia using blunt / sharp dissection +/- hydrodissection with 1 in 200,000 adrenaline Dissect fascia off vaginal epithelium [Optional] Dissect out to pelvic side wall (white line or sacrospinous ligament)	Blunt dissection? Sharp dissection? Hydrodissection with 1 in 200,000 adrenaline? Lateral dissection to white line or sacrospinous ligament?
Graft / mesh inlay	Cut material to size and lay below fascia (inlay, recommended): OR above fascial layer: Size of mesh/graft: [Optional] soak mesh in Rifampicin? OR Other fluid? **ATTACHING THE MESH** Fix at least 2 PDS/Vicryl sutures or 2 non-absorbable sutures to pelvic side wall / coccygeus muscle on each side OR Attach to white line or sacrospinous ligament +/- Capio suturing device	Below fascial layer (**INLAY**), OR above fascial layer (**OVERLAY**) Size of mesh patch:……cm^2 Rifampicin? OR Other fluid?..... PDS to attach mesh? Vicryl to attach mesh? Non-absorbable suture? Attach to white line (ant)? Attach to sacrospinous ligament (post)? Capio suturing device? Yes No
	(for anterior repair): Mesh should also be secured to vault or cervix with a suture(s)	Yes No

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3. Mesh / graft inlay (continued)

Closure	Two-layer closure (PDS or Vicryl): 1. Fascial sutures inserted back from skin edge over mesh/graft **(INLAY)** 2. Skin closed as second layer **(OVERLAY)**	**FASCIA** PDS or Vicryl? Fascial sutures: • continuous locking • continuous non-locking • interrupted? **SKIN** PDS or Vicryl? Skin sutures: • continuous locking • continuous non-locking • interrupted?

4. Vaginal packs and lubricants

Date: **……/……/20…..**	**Procedures**	**Local practice (variations)** ***Please circle or amend***
	Vaginal pack used for up to 24 hours	Yes No
	(If yes) Lubricated?	Oestrogen Proflavine Betadine Dalacin Hibitane Obstetric cream Saline Savlon Aquagel Dry pack

5. POP-Q standardisation

Date: **……/……/20…..**	**Recommended**	**Local practice (variations)** ***Please circle or amend method used most often***
Position	Lithotomy / in leg rests	Lithotomy / in leg rests On back on flat bed or table On side Standing up In theatre / under anaesthetic Sims speculum Plastic speculum (halved) Other
Conditions	Bladder status not specified but recorded	Full bladder Empty bladder Not specified but recorded Bladder status not assessed
	Bowel loading recorded	Bowel loading recorded Bowel loading not recorded
	Full extent of prolapse seen?	Full extent recorded Full extent not recorded
	During Valsalva / pushing down	At rest During Valsalva / pushing down During cough
	Ruler / measuring stick	Ruler / measuring stick Finger measure Estimate by eye

Version 7, 01 August 2011

Appendix 4 Postal questionnaires

Baseline questionnaire

BASELINE QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

BASELINE QUESTIONNAIRE

We are interested in how having prolapse surgery affects your health and everyday life in any way. We would be very grateful if you could complete and return this questionnaire.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Aberdeen
AB25 2ZD
Tel: [redacted]
E-mail: [redacted]

Thank you for taking time to help us with our research.

Funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA)

ISRCTN No: 60695184 **Version 3: 05 November 09**

HOW TO FILL IN THIS QUESTIONNAIRE

Most questions can be answered by putting numbers or a tick in the appropriate box or boxes. Please print your answers carefully within the boxes like this

e.g. | 2 | 7 | **or** | A | N | N | E | **or** | ✓ |

If you make any errors while completing the form, shade out the box completely and mark the correct one like this:

e.g. If you ticked often but meant to answer sometimes:

OFTEN ☐ **SOMETIMES** ☑ **NEVER** ☐

Sometimes the box you tick tells you to skip forward so that you miss out questions which do not apply to you.

Sometimes we would like you to write your answer in your own words, please write these in the boxes provided.

In some questions we would like you to think about different time periods, such as during the last week, during the last 4 weeks or since your prolapse operation. Please check the time periods carefully.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

You do not have to answer any question if you do not want to.

Thank you for your time in completing this questionnaire.

Your answers will be treated with complete confidentiality.

Section A Prolapse symptoms and their effects

Prolapse is a common condition affecting the normal support of the pelvic organs, which results in descent or 'dropping down' of the vaginal walls and/or the pelvic organs themselves. This can include the bladder, the bowel and the womb. Symptoms are usually worse on standing up and straining (e.g. lifting, coughing or exercising) and usually better when lying down and relaxing.

Prolapse may cause a variety of problems. We are trying to find out how many women experience problems from their prolapse, and how much bother it causes. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**. ***(Please tick one box in each row)***

How often during the last four weeks have you had the following symptoms:	Never	Occasion-ally	Some-times	Most of the time	All of the time
A1 a feeling of something coming down from or in your vagina?	☐	☐	☐	☐	☐
A2 an uncomfortable feeling or pain in your vagina which is worse when standing?	☐	☐	☐	☐	☐
A3 a heaviness or dragging feeling in your lower abdomen (tummy)?	☐	☐	☐	☐	☐
A4 a heaviness or dragging feeling in your lower back?	☐	☐	☐	☐	☐
A5 a need to strain (push) to empty your bladder?	☐	☐	☐	☐	☐
A6 a feeling that your bladder has not emptied completely?	☐	☐	☐	☐	☐
A7 a feeling that your bowel has not emptied completely?	☐	☐	☐	☐	☐

A8 **which of the symptoms above (questions A1 to A7) causes you the most bother?** ☐ **Not applicable** ☐

Please enter a number from 1 to 7 in the box, or tick 'Not applicable'

Study Number ☐☐☐☐☐ Baseline Questionnaire

How often during the last four weeks have you had the following symptoms:	Never	Occasionally	Sometimes	Most of the time	All of the time
A9 use your fingers to push up the prolapse to ease discomfort or pain?	☐	☐	☐	☐	☐
A10 take extra measures to ensure the prolapse does not cause personal hygiene problems?	☐	☐	☐	☐	☐

A11 which of the actions above (questions A9 to A10) causes you the most bother? ☐ **Not applicable** ☐

Please enter either 9 to 10 in the box, or tick 'Not applicable'

A12 How long have you been aware that you have a prolapse? ☐☐ Years ☐☐ Months

A13 How long have you been having bothersome symptoms from your prolapse? ☐☐ Years ☐☐ Months Not applicable ☐

A14 Overall, how much do your prolapse symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Section B General health (EQ 5D) TODAY

The next section is about your health **in general**. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today.**

B1 Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

B2 Self-care

- I have no problems with self-care ☐
- I have some problems washing myself or dressing myself ☐
- I am unable to wash or dress myself ☐

B3 Usual activities *(such as work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

B4 Pain/discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

B5 Anxiety/depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Study Number ☐☐☐☐☐ Baseline Questionnaire

Section C | Urine symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many women with prolapse experience urinary symptoms or leak urine, and how much these bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the LAST FOUR WEEKS.

C1 During the night, how many times do you have to get up to urinate (pass water), on average?

- none ☐
- one ☐
- two ☐
- three ☐
- four or more ☐

C2 Do you have a sudden need to rush to the toilet to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C3 Do you have pain in your bladder?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C4 How often do you pass urine during the day?

- 1 to 6 times ☐
- 7 to 8 times ☐
- 9 to 10 times ☐
- 11 to 12 times ☐
- 13 or more times ☐

C5 Is there a delay before you can start to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C6 Do you have to strain to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C7 Do you stop and start more than once while you urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C8 Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C9 Overall, how much do urinary symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Not applicable ☐

Study Number ☐☐☐☐☐ Baseline Questionnaire

C10 Does urine leak before you can get to the toilet (if never, go to section D)?

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

C11 How often do you leak urine?

- ☐ never
- ☐ about once a week or less often
- ☐ two or three times a week
- ☐ about once a day
- ☐ several times a day
- ☐ all the time

C12 We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)?

- ☐ none
- ☐ a small amount
- ☐ a moderate amount
- ☐ a large amount

C13 Does urine leak when you are physically active, exert yourself, cough or sneeze?

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

C14 Do you ever leak urine for no obvious reason and without feeling that you want to go?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C15 Do you leak urine when you are asleep?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C16 Do you leak urine when you have sexual intercourse?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

C17 Overall, how much does leaking urine interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Not applicable ☐

Section D | Bowel symptoms

Many people experience bowel symptoms some of the time. We are trying to find out how many women with prolapse experience bowel symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS.**

D1 On average how many times do you open (move) your bowels?

- four or more times a day ☐
- about one to three times a day ☐
- about once a day ☐
- once every two or three days (two or three times per week) ☐
- once a week or less ☐

D2 Are your stools (faeces, motions) usually…

- watery ☐
- sloppy ☐
- soft and formed ☐
- hard ☐

D3 Do you have to strain to open (move) your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D4 **Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D5 **Do you have to rush to the toilet when you need to open (move) your bowels?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D6 **Do stool (faeces, motion) leak at an inappropriate time or place, or before you can get to the toilet?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D7 **Overall, how much do bowel symptoms interfere with your everyday life?**

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Not applicable ☐

Section E Vaginal and sexual symptoms

Many people experience vaginal or sexual symptoms some of the time. We are trying to find out how many women with prolapse experience vaginal or sexual symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

E1 Are you aware of a dragging pain in your lower abdomen (tummy)?

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

E2 Are you aware of soreness in your vagina?

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

E3 Do you feel that you have reduced sensation or feeling in or around your vagina?

- ☐ not at all
- ☐ a little
- ☐ somewhat
- ☐ a lot

E4 Do you feel that your vagina is too loose or lax?

- ☐ not at all
- ☐ a little
- ☐ somewhat
- ☐ a lot

E5 Are you aware of a lump or bulge coming down in your vagina?

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

E6 Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E7 Do you feel that your vagina is too dry?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E8 Do you have to insert a finger into your vagina to help empty your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E9 Do you feel that your vagina is too tight?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E10 Overall, how much do vaginal symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Not applicable ☐

E11 Do you have a sex life at present?

Yes ☐ If yes, go to E13 No ☐ If no, go to E12

E12 (If you do not have a sex life at present) is it for any of these reasons?

No, because I do not have a partner ☐

No, because of my vaginal symptoms ☐

No, because of my prolapse symptoms ☐

No, because of other reasons (*please specify below)* ☐

E13 Do you have pain when you have sexual intercourse?

not at all ☐

a little ☐

somewhat ☐

a lot ☐

E14 Do worries about your vagina interfere with your sex life?

not at all ☐

a little ☐

somewhat ☐

a lot ☐

E15 Do you feel that your relationship with your partner is affected by vaginal symptoms?

not at all ☐

a little ☐

somewhat ☐

a lot ☐

E16 Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?

Please tick a number between 0 (not at all) and 10 (a great deal)

	0	1	2	3	4	5	6	7	8	9	10	
not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	a great deal

Not applicable ☐

Finally,

Date questionnaire filled in	D	D	M	M	Y	Y	Y	Y
Your date of birth	D	D	M	M	Y	Y	Y	Y

THANK YOU.

Thank you very much for answering these questions.

We intend to use the information you have given us for research to help women like yourself with prolapse.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Tel: [redacted]
E-mail: [redacted]

Thank you again for taking time to help us with our research.

PLEASE BRING THE QUESTIONNAIRE WITH YOU TO HOSPITAL

Six-month questionnaire

6 MONTH QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

6 MONTH QUESTIONNAIRE

We are interested in how your health and everyday life is affected in any way by having prolapse surgery. We would be very grateful if you could complete and return this questionnaire.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Aberdeen
AB25 2ZD
Tel: [redacted]
E-mail: [redacted]

Thank you for taking time to help us with our research.

Funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA)

ISRCTN No: 60695184

Version 3: 05 November 09

Section A Prolapse symptoms and their effects

Prolapse may cause a variety of problems. We are trying to find out how your prolapse problems are now, and how much bother they cause, 6 months after your operation. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS.** ***(Please tick one box in each row)***

How often during the last four weeks have you had the following symptoms:	Never	Occasionally	Sometimes	Most of the time	All of the time
A1 a feeling of something coming down from or in your vagina?	☐	☐	☐	☐	☐
A2 an uncomfortable feeling or pain in your vagina which is worse when standing?	☐	☐	☐	☐	☐
A3 a heaviness or dragging feeling in your lower abdomen (tummy)?	☐	☐	☐	☐	☐
A4 a heaviness or dragging feeling in your lower back?	☐	☐	☐	☐	☐
A5 a need to strain (push) to empty your bladder?	☐	☐	☐	☐	☐
A6 a feeling that your bladder has not emptied completely?	☐	☐	☐	☐	☐
A7 a feeling that your bowel has not emptied completely?	☐	☐	☐	☐	☐

A8 **which of the symptoms above (questions A1 to A7) causes you the most bother?** ☐ **Not applicable** ☐

Please enter a number from 1 to 7 in the box, or tick 'Not applicable'

A9 **Overall, how much do your prolapse symptoms interfere with your everyday life?**

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Section B General health (EQ 5D) TODAY

The next section is about your health in **general**. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today**.

B1 Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

B2 Self-care

- I have no problems with self-care ☐
- I have some problems washing myself or dressing myself ☐
- I am unable to wash or dress myself ☐

B3 Usual activities *(such as work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

B4 Pain/discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

B5 Anxiety/depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Section C | Treatments for symptoms

C1 **Were you re-admitted to hospital, in relation to your prolapse surgery, in the last six months?** Yes ☐ No ☐

If yes to question C1 **how many nights were you readmitted for in total**?
(If you were admitted only as a day case, write 0 in the box provided) ☐☐

C2 **If yes, when and why were you re-admitted?** *(Please give details of all re-admissions):*

Finally,

Date questionnaire filled in	D D	M M	Y Y Y Y
Your date of birth	D D	M M	Y Y Y Y

THANK YOU

Thank you very much for being part of the PROSPECT study and for your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to advise women and doctors about prolapse surgery in the future. It will be treated with the strictest confidence and kept securely.

Please send the questionnaire back to us in Aberdeen in the envelope provided.

We hope to contact you again in the future to check on how your health is after your prolapse surgery

One-year questionnaire

ONE YEAR QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

ONE YEAR QUESTIONNAIRE

We are interested in how having prolapse surgery affects your health and everyday life in any way. We would be very grateful if you could complete and return this questionnaire.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Aberdeen
AB25 2ZD
Tel: [redacted]
E-mail: [redacted]

Thank you for taking time to help us with our research.

Funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA)

ISRCTN No:60695184

Version 3: 06 November 09

HOW TO FILL IN THIS QUESTIONNAIRE

Most questions can be answered by putting numbers or a tick in the appropriate box or boxes. Please print your answers carefully within the boxes like this

e.g. | 2 | 7 | or | A | N | N | E | or | ✓ |

If you make any errors while completing the form, shade out the box completely and mark the correct one like this:

e.g. If you ticked often but meant to answer sometimes:

OFTEN ☐ SOMETIMES ☑ NEVER ☐

Sometimes the box you tick tells you to skip forward so that you miss out questions which do not apply to you.

Sometimes we would like you to write your answer in your own words, please write these in the boxes provided.

In some questions we would like you to think about different time periods, such as during the last week, during the last 4 weeks or since your prolapse operation. Please check the time periods carefully.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

You do not have to answer any question if you do not want to.

Thank you for your time in completing this questionnaire.

Your answers will be treated with complete confidentiality.

Please start here:

Date questionnaire filled in	D	D	M	M	Y	Y	Y	Y
Your date of birth	D	D	M	M	Y	Y	Y	Y

Section A Prolapse symptoms and their effects

Prolapse may cause a variety of problems. We are trying to find out how your prolapse problems are now, and how much bother they cause, one year after your operation. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**. ***(Please tick one box in each row)***

How often during the last four weeks have you had the following symptoms:	Never	Occasion-ally	Some-times	Most of the time	All of the time
A1 a feeling of something coming down from or in your vagina?	☐	☐	☐	☐	☐
A2 an uncomfortable feeling or pain in your vagina which is worse when standing?	☐	☐	☐	☐	☐
A3 a heaviness or dragging feeling in your lower abdomen (tummy)?	☐	☐	☐	☐	☐
A4 a heaviness or dragging feeling in your lower back?	☐	☐	☐	☐	☐
A5 a need to strain (push) to empty your bladder?	☐	☐	☐	☐	☐
A6 a feeling that your bladder has not emptied completely?	☐	☐	☐	☐	☐
A7 a feeling that your bowel has not emptied completely?	☐	☐	☐	☐	☐

A8 **which of the symptoms above (questions A1 to A7) causes you the most bother?** ☐ **Not applicable** ☐

Please enter a number from 1 to 7 in the box, or tick 'Not applicable'

A9 **Overall, how much do your prolapse symptoms interfere with your everyday life?**

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Study Number ☐☐☐☐☐

One Year Questionnaire

Section B General health (EQ 5D) TODAY

The next section is about your health **in general**. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today.**

B1 Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

B2 Self-care

- ☐ I have no problems with self-care
- ☐ I have some problems washing myself or dressing myself
- ☐ I am unable to wash or dress myself

B3 Usual activities *(such as work, study, housework, family or leisure activities)*

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

B4 Pain/discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

B5 Anxiety/depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

Section C Treatments since your prolapse operation

C1 **Have you had a new prolapse operation since your operation one year ago?** Yes ☐ No ☐

If yes, please give details, eg what operation and when?

C2 **Have you had a new operation for leaking urine since your prolapse operation one year ago?** Yes ☐ No ☐

If yes, please give details, eg what operation and when?

C3 **Have you had any stitches removed from the site of your prolapse operation one year ago?**

Yes ☐ No ☐ Don't know ☐

C4 **Have you had any mesh removed from the site of your prolapse operation one year ago?**

Yes ☐ No ☐ Don't know ☐

C5 **In the last six months were you re-admitted to hospital for any other reason, in relation to your prolapse surgery one year ago?** Yes ☐ No ☐

If yes to question C5 **how many nights were you readmitted for in total***?*
If you were admitted only as a day case, write 0 in the box: ☐

C6 **If yes, when and why were you re-admitted?** *(Please give details):*

C7 **Are you using absorbent pads for leakage of urine?** Yes ☐ No ☐

C8 **Are you using a permanent catheter (inside your bladder) to collect urine?** Yes ☐ No ☐

C9 **Do you ever use a disposable or reusable (intermittent) catheter to help you to empty your bladder?** Yes ☐ No ☐

C10 **Were you prescribed any medicines by a doctor or nurse, in relation to your prolapse symptoms, in the last year?** Yes ☐ No ☐

C11 **Have you had any other treatment for prolapse or leaking urine?**
If yes to question C10 or 11, please tick all treatments you have had in question C12 Yes ☐ No ☐

C12 **Please tick all prescribed medicines or other treatments for prolapse or leaking urine that you have had since your operation**

Oestrogen treatment (eg vaginal cream, HRT) ☐

Drug treatment for bladder problems or leaking urine (please give details) ☐

A ring pessary inserted ☐

A shelf pessary inserted ☐

Any other treatment for prolapse or another gynae problem (please give details) ☐

Details:

C13 **If you are in paid employment, how many days off sick have you had in the last year?** *(If you are not in paid employment, please ignore this question)* ☐

C14 **Have you seen your GP, in relation to your prolapse, in the last year?** Yes ☐ No ☐

If yes to question C14, how many times did you see your GP? ☐

C15 **Have you seen a practice nurse in relation to your prolapse in the last year?** Yes ☐ No ☐

If yes to question C15, how many times did you see the nurse? ☐

C16 Have you visited hospital outpatients to see a doctor, in relation to your prolapse, in the last year? Yes ☐ No ☐

If yes to question C16, how many times did you visit outpatients? ☐

C17 Have you seen a physiotherapist, in relation to your prolapse, in the last six months? Yes ☐ No ☐

If yes to question C17, how many times did you see the physiotherapist? ☐

C18 Have you visited any other health care professional, in relation to your prolapse, in the last year? Yes ☐ No ☐

If yes to question C18, specify whom you have seen and the number of times you have seen them in the boxes provided:

Other *(please specify)*: ☐ Times ☐

C19 Did you buy any medicines over the counter to treat your prolapse symptoms in the last year? Yes ☐ No ☐

C20 If yes to C19 above, how much in total did you spend? £ ☐ .

C21 Did you pay to see any private health care professional, in relation to your prolapse, in the last year? Yes ☐ No ☐

C22 Have you paid for any other healthcare, in relation to your prolapse, in the last year? Yes ☐ No ☐

C23 If yes to C21 or C22 above, how much did you spend? £ ☐ .

THANK YOU

Thank you very much for being part of the PROSPECT study and your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to advise women and doctors about prolapse surgery in the future. It will be treated with the strictest confidence and kept securely.

Please send the questionnaire back to us in Aberdeen in the envelope provided.

We hope to contact you again in the future to check on how your health is after your prolapse surgery.

One-year additional questionnaire

ONE YEAR ADDITIONAL QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

ONE YEAR ADDITIONAL QUESTIONNAIRE

We are interested in how having prolapse surgery affects your health and everyday life in any way. We would be very grateful if you could complete and return this questionnaire.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Tel: [redacted]
E-mail: [redacted]

Thank you for taking time to help us with our research.

Funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA)

ISRCTN No: 60695184 **Version 3: 05 November 09**

Please start here:

Date questionnaire filled in	D	D	M	M	Y	Y	Y	Y
Your date of birth	D	D	M	M	Y	Y	Y	Y

Section A Urine symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many women with prolapse experience urinary symptoms or leak urine, and how much these bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **LAST FOUR WEEKS**.

A1 During the night, how many times do you have to get up to urinate (pass water), on average?

- none ☐
- one ☐
- two ☐
- three ☐
- four or more ☐

A2 Do you have a sudden need to rush to the toilet to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A3 Do you have pain in your bladder?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A4 How often do you pass urine during the day?

- 1 to 6 times ☐
- 7 to 8 times ☐
- 9 to 10 times ☐
- 11 to 12 times ☐
- 13 or more times ☐

A5 Is there a delay before you can start to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A6 Do you have to strain to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A7 Do you stop and start more than once while you urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A8 Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

Study Number ☐☐☐☐☐

One Year Additional Questionnaire

A9 Overall, how much do urinary symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

A10 Does urine leak before you can get to the toilet (if never, go to section B)?

never ☐
occasionally ☐
sometimes ☐
most of the time ☐
all of the time ☐

A11 How often do you leak urine?

never ☐
about once a week or less often ☐
two or three times a week ☐
about once a day ☐
several times a day ☐
all the time ☐

A12 We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)?

none ☐
a small amount ☐
a moderate amount ☐
a large amount ☐

A13 Does urine leak when you are physically active, exert yourself, cough or sneeze?

never ☐
occasionally ☐
sometimes ☐
most of the time ☐
all of the time ☐

A14 Do you ever leak urine for no obvious reason and without feeling that you want to go?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A15 Do you leak urine when you are asleep?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

A16 Do you leak urine when you have sexual intercourse?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

A17 Overall, how much does leaking urine interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Study Number ☐☐☐☐☐

One Year Additional Questionnaire

Section B Bowel symptoms

Many people experience bowel symptoms some of the time. We are trying to find out how many women with prolapse experience bowel symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS.**

B1 On average how many times do you open (move) your bowels?

- four or more times a day ☐
- about one to three times a day ☐
- about once a day ☐
- once every two or three days (two or three times per week) ☐
- once a week or less ☐

B2 Are your stools (faeces, motions) usually…

- watery ☐
- sloppy ☐
- soft and formed ☐
- hard ☐

B3 Do you have to strain to open (move) your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

B4 Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

B5 Do you have to rush to the toilet when you need to open (move) your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

B6 Do stool (faeces, motion) leak at an inappropriate time or place, or before you can get to the toilet?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

B7 Overall, how much do bowel symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Section C Vaginal and sexual symptoms

Many people experience vaginal or sexual symptoms some of the time. We are trying to find out how many women with prolapse experience vaginal or sexual symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

C1 Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C2 Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C3 Are you aware of a dragging pain in your lower abdomen (tummy)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C4 Are you aware of soreness in your vagina?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C5 **Do you feel that you have reduced sensation or feeling in or around your vagina?**

- ☐ not at all
- ☐ a little
- ☐ somewhat
- ☐ a lot

C6 **Do you feel that your vagina is too loose or lax?**

- ☐ not at all
- ☐ a little
- ☐ somewhat
- ☐ a lot

C7 **Are you aware of a lump or bulge coming down in your vagina?**

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

C8 **Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?**

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

C9 **Do you feel that your vagina is too dry?**

- ☐ never
- ☐ occasionally
- ☐ sometimes
- ☐ most of the time
- ☐ all of the time

C10 Do you have to insert a finger into your vagina to help empty your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C11 Do you feel that your vagina is too tight?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

C12 Overall, how much do vaginal symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

C13 Do you have a sex life at present?

Yes ☐ If yes, go to C15 No ☐ If no, go to C14

C14 (If you do not have a sex life at present) is it for any of these reasons?

- No, because I do not have a partner ☐
- No, because of my vaginal symptoms ☐
- No, because of my prolapse symptoms ☐
- No, because of other reasons (*please specify below)* ☐

C15 Do you have pain when you have sexual intercourse?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

C16 Do worries about your vagina interfere with your sex life?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

C17 Do you feel that your relationship with your partner is affected by vaginal symptoms?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

C18 Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Section D General information

D1 **After your prolapse surgery a year ago, how long was it before you were able to get back to your normal daily activities?**

Enter number of months ☐

D2 **Please describe how your prolapse is now, compared with how it was before you had surgery one year ago:**

- very much better ☐
- much better ☐
- a little better ☐
- no change ☐
- a little worse ☐
- much worse ☐
- very much worse ☐

D3 **Overall how satisfied are you with the results of the operation**

- completely satisfied ☐
- fairly satisfied ☐
- fairly dissatisfied ☐
- very dissatisfied ☐
- not sure ☐

D4 **Would you recommend this operation to a friend?** Yes ☐ No ☐

THANK YOU

Thank you very much for being part of the PROSPECT study and your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to advise women and doctors about prolapse surgery in the future. It will be treated with the strictest confidence and kept securely.

Please send the questionnaire back to us in Aberdeen in the envelope provided.

We hope to contact you again in the future to check on how your health is after your prolapse surgery.

Patient costs questionnaire

PARTICIPANT COSTS QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PARTICIPANT COSTS QUESTIONNAIRE

Thank you for helping us with our research into prolapse surgery. We would be very grateful if you could complete and return this questionnaire.

Thank you for taking the time to help us with our research.

ISRCTN60695184

Version 2 01 July 2011

This questionnaire will help us to find out how much it costs you to use health services. We wish to ask about your **most recent** admission to hospital, your **most recent** outpatient appointment and your **most recent** appointment with a GP. We wish to know how much money and time were spent by you and any companion in attending these appointments and as a result of any hospital admission you may have had.

It may have been a long time ago and we understand that you are unlikely to remember the exact details. Please just give us your best guess.

If you have a problem in answering any question please telephone the PROSPECT Study Office on [redacted]. Please return the questionnaire in the enclosed pre-paid envelope.

Section A | Your most recent admission to hospital

If in the last 12 months you were not admitted to hospital please go to Section B

1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the **main** (longest in terms of distance) part of your journey.

Walked	1	Taxi	5
Cycled	2	Hospital car	6
Bus	3	Ambulance	7
Train	4	Private car	8

Other (please specify) _____ 9

2. If you travelled by bus, train or taxi to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare. If you purchased a return ticket, please put half the cost of your ticket.

Cost of (one-way) fare (£) ☐☐ - ☐☐ pence

3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way ☐☐☐

4. If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.

Expenditure on parking fee (£) ☐☐ - ☐☐ Pence

5. When you were admitted to the hospital, how long did you spend there? Please write the number of days in the box below.

Number of days ☐☐

6. What would you otherwise have been doing as your **main** activity if you had not had to be admitted to hospital? Please circle the number that best applies to you.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4		

Other (please specify) _____ 8

Study Number ☐☐☐☐☐ Participant Costs Questionnaire

7. When you were admitted to hospital, did anyone come with you? Please circle the appropriate response.

Yes (continue with question 8).....1 No (go to section B).....2

8. Who accompanied you to the hospital? Please circle the number that best describes the main person who accompanied you to the hospital.

Partner/spouse.....1 Paid caregiver.....3

Other relative.....2 Friend.....4

Other (please specify) [ ] 5

9. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the hospital.

Housework.....1 Paid work.....5

Childcare.....2 Voluntary work.....6

Caring for a relative or friend.....3 Leisure activities.....7

Unemployed.....4

Other (please specify) [ ] 8

10. Did your main companion take time off from paid work (or business activity if self-employed)? Please circle the appropriate response.

Yes (continue with question 11).....1 No (go to section B).....2

11. Please write the number of hours your companion took off from paid work (or business activity if self-employed) in the box below. Please put zero if your main companion did not take time off from paid work (or business activity if self-employed) to accompany you to the hospital.

Number of hours [ ][ ]

12. Whilst you were in hospital, approximately how many times did your main companion come to visit you?

Number of times [ ][ ]

Section B Your most recent outpatient visit

If in the last 12 months you did not have an outpatients appointment please go to Section C

1. Please circle the number that best describes how you travelled. If you used more than one form of transport please indicate the way you travelled for the **main** (longest in terms of distance) part of your journey.

Walked	1	Taxi	5
Cycled	2	Hospital car	6
Bus	3	Ambulance	7
Train	4	Private car	8

Other (please specify) _____ 9

2. If you travelled by bus, taxi or train to hospital what was the total cost of the (one-way) journey? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi at all or if you did not pay a fare. If you purchased a return ticket, please put half the cost of the return ticket.

Cost of (one-way) fare (£) ☐☐ - ☐☐ pence

3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way ☐☐☐

4. If you travelled by private car and you or your companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay a parking fee.

Expenditure on parking fee (£) ☐☐ - ☐☐ Pence

5. When you visited outpatients, how long did it take to travel there? Please write the number of hours and minutes in the box below.

Number of hours ☐☐ - ☐☐ minutes

6. When you visited outpatients, how long did you spend there? Please write the number of hours and minutes in the box below.

Number of hours ☐☐ - ☐☐ minutes

7. Please circle the number that best describes what you otherwise would have been doing as your main activity if you had not been visiting outpatients?

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4		

Other (please specify) _____ 8

8. When you visited outpatients did anyone come with you? Please circle the appropriate response.

Yes (continue with question 9)	1	No (go to section C)	2

9. Please circle the number that best describes the main person who accompanied you to outpatients.

Partner/spouse	1	Paid caregiver	3
Other relative	2	Friend	4

Other (please specify) _____ 5

10. If your main companion travelled with you by bus or train approximately how much did they pay (one-way) in fares? Please write the approximate cost in the box below. Please put zero if your main companion did not travel by bus or train at all. If they purchased a return ticket, please put half the cost of the return ticket.

Cost of (one-way) fare (£) [ ][ ] - [ ][ ] pence

11. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to outpatients.

Housework	1	Paid work	5
Childcare	2	Voluntary work	6
Caring for a relative or friend	3	Leisure activities	7
Unemployed	4		

Other (please specify) _____ 8

Section C | Your most recent GP appointment

1. Please circle the number that best describes how you travelled to your GP appointment. If you used more than one form of transport please indicate the way you travelled for the **main** (longest in terms of distance) part of your journey.

Walked	1	Taxi	5
Cycled	2	Hospital car	6
Bus	3	Ambulance	7
Train	4	Private car	8

Other (please specify) [ ] 9

2. If you travelled by bus, train or taxi, what was the cost of the (one-way) fare? Please write the cost in the box below. Please put zero if you did not travel by bus, train or taxi or if you did not pay the fare. If you purchased a return ticket, please put half the cost of the return ticket.

Cost of (one-way) fare (£) [ ][ ] - [ ][ ] pence

3. If you travelled by private car about how many miles did you travel one-way? Please write the number of miles in the box below. Please put zero if you did not travel by private car at all.

Number of miles one-way [ ][ ][ ]

4. If you travelled by private car and you or a companion had to pay a parking fee how much did this cost? Please write the cost in the box below. Please put zero if you did not pay for parking.

Expenditure on parking fee (£) [ ][ ] - [ ][ ] Pence

5. When you visited the GP, how long did it take to travel there? Please write the number of minutes in the box below.

Number of minutes [ ][ ]

6. When you visited the GP, how long did you spend there? Please write the number of minutes in the box below. Please include in your answer the time spent waiting and also the time spent with the doctors and nurses

Number of minutes [ ][ ]

7. Please circle the number that best describes what you otherwise would have been doing as your main activity if you had not visited the GP.

Housework 1	Paid work 5
Childcare 2	Voluntary work 6
Caring for a relative or friend 3	Leisure activities 7
Unemployed 4	

Other (please specify) _____ 8

8. When you visited the GP did anyone come with you? Please circle the appropriate response.

Yes (continue with question 9) 1	No (go to the end) 2

9. Please circle the number(s) that best describe the person(s) who accompanied you to the GP's surgery. You may circle more than one response if appropriate.

Partner/spouse 1	Paid caregiver 3
Other relative 2	Friend 4

Other (please specify) _____ 5

10. If your main companion travelled with you by bus or train how much approximately did they pay (one-way) in fares (if anything)? Please write the cost in the box below. Please put zero if your main companion did not travel by bus or train at all. If they purchased a return ticket, please put half the cost of the return ticket.

Cost of (one-way) fare (£) [ ][ ] - [ ][ ] pence

11. Please circle the number that best describes what your main companion would otherwise have been doing as their main activity if they had not gone with you to the GP's surgery.

Housework 1	Paid work 5
Childcare 2	Voluntary work 6
Caring for a relative or friend 3	Leisure activities 7
Unemployed 4	

Other (please specify) _____ 5

If you wish to provide any further information please do so below.

Thank you for filling in this questionnaire, please post it back to us in the envelope provided

Two-year questionnaire

TWO YEAR QUESTIONNAIRE

CONFIDENTIAL

Participant Study No

PROSPECT
PROLAPSE SURGERY: PRAGMATIC EVALUATION AND RANDOMISED CONTROLLED TRIALS

TWO YEAR QUESTIONNAIRE

We are interested in how having prolapse surgery affects your health and everyday life in any way. We would be very grateful if you could complete and return this questionnaire.

If you would like any further information or have any queries about the study, please contact:

PROSPECT Study Office
Tel: [redacted]
E-mail: [redacted]

Thank you for taking time to help us with our research.

Funded by the National Institute for Health Research Health Technology Assessment programme (NIHR HTA)

ISRCTN No: 60695184 **Version 3: 09 November 09**

HOW TO FILL IN THIS QUESTIONNAIRE

Most questions can be answered by putting numbers or a tick in the appropriate box or boxes. Please print your answers carefully within the boxes like this

e.g. | 2 | 7 | **or** | A | N | N | E | **or** | ✓ |

If you make any errors while completing the form, shade out the box completely and mark the correct one like this:

e.g. If you ticked often but meant to answer sometimes:

OFTEN ☐ **SOMETIMES** ☑ **NEVER** ☐

Sometimes the box you tick tells you to skip forward so that you miss out questions which do not apply to you.

Sometimes we would like you to write your answer in your own words, please write these in the boxes provided.

In some questions we would like you to think about different time periods, such as during the last week, during the last 4 weeks or since your prolapse operation. Please check the time periods carefully.

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

You do not have to answer any question if you do not want to.

Thank you for your time in completing this questionnaire.

Your answers will be treated with complete confidentiality.

Please start here:

Date questionnaire filled in	D	D	M	M	Y	Y	Y	Y
Your date of birth	D	D	M	M	Y	Y	Y	Y

Study Number | | | | | |

Two Year Questionnaire

Section A Prolapse symptoms and their effects

Prolapse may cause a variety of problems. We are trying to find out how your prolapse problems are now, and how much bother they cause, two years after your operation. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**. ***(Please tick one box in each row)***

How often during the last four weeks have you had the following symptoms:	Never	Occasionally	Sometimes	Most of the time	All of the time
A1 a feeling of something coming down from or in your vagina?	☐	☐	☐	☐	☐
A2 an uncomfortable feeling or pain in your vagina which is worse when standing?	☐	☐	☐	☐	☐
A3 a heaviness or dragging feeling in your lower abdomen (tummy)?	☐	☐	☐	☐	☐
A4 a heaviness or dragging feeling in your lower back?	☐	☐	☐	☐	☐
A5 a need to strain (push) to empty your bladder?	☐	☐	☐	☐	☐
A6 a feeling that your bladder has not emptied completely?	☐	☐	☐	☐	☐
A7 a feeling that your bowel has not emptied completely?	☐	☐	☐	☐	☐

A8 **which of the symptoms above (questions A1 to A7) causes you the most bother?** ☐ **Not applicable** ☐

Please enter a number from 1 to 7 in the box, or tick 'Not applicable'

A9 **Overall, how much do your prolapse symptoms interfere with your everyday life?**

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Section B General health (EQ 5D) TODAY

The next section is about your health **in general**. By placing a tick in one box in each group below, please indicate which statements best describe your own health state **today.**

B1 Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

B2 Self-care

I have no problems with self-care ☐

I have some problems washing myself or dressing myself ☐

I am unable to wash or dress myself ☐

B3 Usual activities *(such as work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

B4 Pain/discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

B5 Anxiety/depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Study Number ☐☐☐☐☐

Two Year Questionnaire

Section C Treatments for symptoms

C1 **In the last year, have you had a new prolapse operation?** Yes ☐ No ☐
If yes, please give details, eg what operation and when?

C2 **Are you now on the waiting list for a new prolapse operation?** Yes ☐ No ☐

C3 **In the last year, have you had a new operation for leaking urine?** Yes ☐ No ☐
If yes, please give details, eg what operation and when?

C4 **Are you now on the waiting list for a new operation for leaking urine?** Yes ☐ No ☐

C5 **In the last year, have you had any stitches removed from the site of your prolapse operation?**
Yes ☐ No ☐ Don't know ☐

C6 **In the last year, have you had any mesh removed from the site of your prolapse operation?**
Yes ☐ No ☐ Don't know ☐

C7 **In the last year, were you re-admitted to hospital for any other reason, in relation to your prolapse surgery two years ago?** Yes ☐ No ☐

If yes to question C7 **how many nights were you readmitted for in total***?*
(If you were admitted only as a day case, write 0 in the box provided)

C8 **If yes, why were you re-admitted?** *(Please give details of all re-admissions):*

C9 **Are you using absorbent pads for leakage of urine?** Yes ☐ No ☐

C10 **Are you using a permanent catheter (inside your bladder) to collect urine?** Yes ☐ No ☐

C11 **Do you ever use a disposable or reusable (intermittent) catheter to help you to empty your bladder?** Yes ☐ No ☐

C12 **Were you prescribed any medicines by a doctor or nurse, in relation to your prolapse symptoms, in the last year?** Yes ☐ No ☐

C13 **Have you had any other treatment for prolapse or leaking urine?** Yes ☐ No ☐

If yes to question C12 or 13, please tick all treatments you have had in question C14

C14 **Please tick all prescribed medicines or other treatments for prolapse or leaking urine that you have had since your operation**

Oestrogen treatment (eg vaginal cream, HRT) ☐

Drug treatment for bladder problems or leaking urine (please give details) ☐

A ring pessary inserted ☐

A shelf pessary inserted ☐

Any other treatment for prolapse or another gynae problem (please give details) ☐

Details:

C15 **If you are in paid employment, how many days off sick have you had in the last year?** *(If you are not in paid employment, please ignore this question)* ☐

C16 **Have you seen your GP, in relation to your prolapse, in the last year?** Yes ☐ No ☐

If yes to question C16, how many times did you see your GP? ☐

C17 **Have you seen a practice nurse in relation to your prolapse in the last year?** Yes ☐ No ☐

If yes to question C17, how many times did you see the nurse? ☐

Study Number ☐☐☐☐☐ Two Year Questionnaire

C18 Have you visited hospital outpatients to see a doctor, in relation to your prolapse, in the last year? Yes ☐ No ☐

If yes to question C18, how many times did you visit outpatients?

C19 Have you seen a physiotherapist, in relation to your prolapse, in the last year? Yes ☐ No ☐

If yes to question C19, how many times did you see the physiotherapist?

C20 Have you visited any other health care professional, in relation to your prolapse, in the last year? Yes ☐ No ☐

If yes to question C20, specify whom you have seen and the number of times you have seen them in the boxes provided:

Other *(please specify):* Times

C21 Did you buy any medicines over the counter to treat your prolapse symptoms in the last year? Yes ☐ No ☐

C22 If yes to C21 above, how much in total did you spend? £ .

C23 Did you pay to see any private health care professional, in relation to your prolapse, in the last year? Yes ☐ No ☐

C24 Have you paid for any other healthcare, in relation to your prolapse, in the last year? Yes ☐ No ☐

C25 If yes to C23 or C24 above, how much did you spend? £ .

Section D Urine symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many women with prolapse experience urinary symptoms or leak urine, and how much these bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **LAST FOUR WEEKS**.

D1 During the night, how many times do you have to get up to urinate (pass water), on average?

- none ☐
- one ☐
- two ☐
- three ☐
- four or more ☐

D2 Do you have a sudden need to rush to the toilet to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D3 Do you have pain in your bladder?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D4 How often do you pass urine during the day?

- 1 to 6 times ☐
- 7 to 8 times ☐
- 9 to 10 times ☐
- 11 to 12 times ☐
- 13 or more times ☐

Study Number ☐☐☐☐☐

Two Year Questionnaire

D5 Is there a delay before you can start to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D6 Do you have to strain to urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D7 Do you stop and start more than once while you urinate (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D8 Do you have to use your fingers to push up the prolapse to help empty your bladder (pass water)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D9 Overall, how much do urinary symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

D10 Does urine leak before you can get to the toilet (if never, go to section E)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D11 How often do you leak urine?

- never ☐
- about once a week or less often ☐
- two or three times a week ☐
- about once a day ☐
- several times a day ☐
- all the time ☐

D12 We would like to know how much urine you think leaks. How much urine do you usually leak (whether you wear protection or not)?

- none ☐
- a small amount ☐
- a moderate amount ☐
- a large amount ☐

D13 Does urine leak when you are physically active, exert yourself, cough or sneeze?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D14 Do you ever leak urine for no obvious reason and without feeling that you want to go?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D15 Do you leak urine when you are asleep?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

D16 Do you leak urine when you have sexual intercourse?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

D17 Overall, how much does leaking urine interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Section E Bowel symptoms

Many people experience bowel symptoms some of the time. We are trying to find out how many women with prolapse experience bowel symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS.**

E1 On average how many times do you open (move) your bowels?

- four or more times a day ☐
- about one to three times a day ☐
- about once a day ☐
- once every two or three days (two or three times per week) ☐
- once a week or less ☐

E2 Are your stools (faeces, motions) usually…

- watery ☐
- sloppy ☐
- soft and formed ☐
- hard ☐

E3 Do you have to strain to open (move) your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E4 **Do you have to insert a finger into your back passage to help empty stool (faeces, motion) from your bowel?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E5 **Do you have to rush to the toilet when you need to open (move) your bowels?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E6 **Do stool (faeces, motion) leak at an inappropriate time or place, or before you can get to the toilet?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

E7 **Overall, how much do bowel symptoms interfere with your everyday life?**

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Section F Vaginal and sexual symptoms

Many people experience vaginal or sexual symptoms some of the time. We are trying to find out how many women with prolapse experience vaginal or sexual symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**.

F1 Do you have to insert a finger into your vagina to push up the prolapse to ease discomfort or pain?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F2 Do you have to take extra measures to ensure the prolapse does not cause personal hygiene problems?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F3 Are you aware of a dragging pain in your lower abdomen (tummy)?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F4 Are you aware of soreness in your vagina?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F5 **Do you feel that you have reduced sensation or feeling in or around your vagina?**

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

F6 **Do you feel that your vagina is too loose or lax?**

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

F7 **Are you aware of a lump or bulge coming down in your vagina?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F8 **Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F9 **Do you feel that your vagina is too dry?**

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F10 Do you have to insert a finger into your vagina to help empty your bowels?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F11 Do you feel that your vagina is too tight?

- never ☐
- occasionally ☐
- sometimes ☐
- most of the time ☐
- all of the time ☐

F12 Overall, how much do vaginal symptoms interfere with your everyday life?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

F13 Do you have a sex life at present?

Yes ☐ If yes, go to F15 No ☐ If no, go to F14

F14 (If you do not have a sex life at present) is it for any of these reasons?

- No, because I do not have a partner ☐
- No, because of my vaginal symptoms ☐
- No, because of my prolapse symptoms ☐
- No, because of other reasons (*please specify below)* ☐

Now go to Section G

F15 Do you have pain when you have sexual intercourse?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

F16 Do worries about your vagina interfere with your sex life?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

F17 Do you feel that your relationship with your partner is affected by vaginal symptoms?

- not at all ☐
- a little ☐
- somewhat ☐
- a lot ☐

F18 Overall, how much do you feel that your sex life has been spoilt by vaginal symptoms?

Please tick a number between 0 (not at all) and 10 (a great deal)

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Not applicable ☐

Section G General information

G1 Please describe how your prolapse is now, compared with how it was before you had surgery two years ago:

- very much better ☐
- much better ☐
- a little better ☐
- no change ☐
- a little worse ☐
- much worse ☐
- very much worse ☐

G2 Overall how satisfied are you with the results of the operation

- completely satisfied ☐
- fairly satisfied ☐
- fairly dissatisfied ☐
- very dissatisfied ☐
- not sure ☐

G3 Would you recommend this operation to a friend? Yes ☐ No ☐

THANK YOU

Thank you very much for being part of the PROSPECT study and your time and patience in filling in this questionnaire.

The information you have given us will be extremely useful in helping us to advise women and doctors about prolapse surgery in the future. It will be treated with the strictest confidence and kept securely.

Please send the questionnaire back to us in Aberdeen in the envelope provided.

We hope to contact you again in the future to check on how your health is after your prolapse surgery.

Appendix 5 Statistical analysis plan

STATISTICAL ANALYSIS PLAN

Prepared by:

G. MacLennan _____ 14/08/2014_

(date)

Trial Statistician

Approved by:

C. Glazener _____

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Chief Investigator

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_____

(date)

CHaRT Director

ISRCTN60695184

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Study Design

PROSPECT is a multi-centred randomised control trial with a parallel-cohort design. The aim of the study is to investigate the safety, effectiveness and cost-effectiveness of operations for women with pelvic organ prolapse. The study includes two RCTs within a Comprehensive Cohort Study, with the following principle objectives:

In women having a primary prolapse repair, the effects of a standard repair versus the following:

1) Standard repair using a biological graft inlay
2) Standard repair using a non-absorbable or combined mesh inlay

In women having a secondary prolapse repair, the effects of a standard repair versus the following:

3) Standard repair using a non-absorbable or combined mesh inlay
4) Mesh kit procedure

Treatment allocation is minimised by age (>60/60+), type of planned prolapse surgery (anterior/posterior/both), concomitant continence procedure and concomitant prolapse procedure. Treatment allocations are summarised in Figure 1.

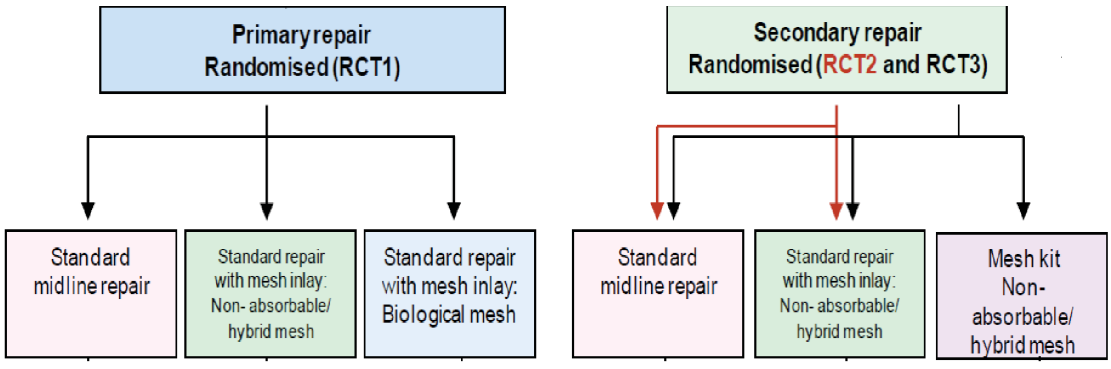

Figure 1. Treatment allocation in PROSPECT RCTs

Since recruitment began, additional randomisation menu options have been made available, partly as a result of some mesh types being unavailable on

certain days. It is possible in RCT1 to randomise just between standard repair and non-absorbable mesh (RCT1B), or between standard repair and biological mesh (RCT1C). In the secondary trial, an additional menu option of randomising between standard repair and mesh kit has been added (RCT2D).

At close of recruitment (August 2013), there were 36 participating centres throughout the UK. The centres are listed in Table 1.

Table 11– PROSPECT participating centres

Aberdeen	Cumbria	Maidstone	Rotherham
Ayrshire & Arran	Derby	Manchester	South Devon
Barnsley	Exeter	Mid Yorkshire	South Tees (Friarage)
Birmingham	Harrogate	Middlesex	South Tees (James Cook)
Bolton	Huddersfield	North Devon	Sunderland
Bradford	Hull	Nottingham	Taunton
Brighton	Imperial	Plymouth	Whipps Cross
Bristol	Leicester	Portsmouth	Wolverhampton
Chester	Luton & Dunstable	Preston	York

Outcome Measures

All outcome measures are recorded at baseline, 12 months and 24 months.

Primary Outcomes

The primary patient-reported outcomes are symptoms of prolapse, measured as:

- the number and frequency of prolapse symptoms on the Pelvic Organ Prolapse Symptom Scale (POP-SS)[1] at one year after surgery
- a quality of life outcome measured as the overall effect of prolapse symptoms on everyday life.

The POP-SS is a composite outcome measure comprising seven patient recorded items each relating to a different symptom. Each item has an ordinal response schedule with five levels of response based on frequency of the symptom ("never", "occasionally", sometimes", "most of the time" and "all of the time") and is scored from 0 to 4 respectively. The overall POP-SS score is the sum of each item score and can range from zero to 28.

For the primary analysis, individual items that are missing will be assumed to have a value of zero. However, this assumption will be tested in sensitivity analyses. If all seven questions are unanswered, then the POP-SS score will be treated as missing.

The primary economic outcome measure of cost effectiveness is incremental cost per QALY (QALYs based on the EQ-5D[2]). The cost effectiveness analysis is set out separately in the economic analysis plan.

Secondary Outcomes

General

- immediate and late post-operative morbidity (injury to organs, excess blood loss, blood transfusion, infection (UTI, sepsis, abscess), pain, urinary retention, constipation)
- other adverse effects or complications including mesh erosion or removal
- operating time
- blood loss
- number of nights in hospital
- time until resumption of usual activities

Prolapse outcomes

- subjective recurrence of prolapse
- subjective continuation / recurrence of prolapse symptoms
- objective residual prolapse stage (POP-Q) at original site
- development of new (*de novo*) prolapse at another site
- need for other conservative prolapse treatment (e.g. PFMT, mechanical device)
- need for further surgery for prolapse and/or for urinary incontinence
- time to further surgery
- satisfaction with surgery

Urinary outcomes

- Urinary incontinence (persistent or de novo, and types of incontinence)
- Need for alternative management for incontinence (e.g. PFMT, mechanical devices, pads, surgery, drugs, intermittent catheterisation)

Bowel outcomes

- Constipation (persistent or de novo)
- Bowel urgency (persistent or de novo)
- Faecal incontinence (persistent or de novo)

Vaginal symptoms and sexual function outcomes

- Vaginal symptoms

- Dyspareunia / apareunia / difficulty with intercourse (persistent or de novo)

Quality of life outcome measures

- Condition-specific quality of life measures (urinary, bowel, vaginal, sexual)
- General health measure (EQ-5D[2])

Missing data

Loss to follow-up

Complete loss to follow-up is defined as a participant who has no information on outcomes at any follow-up timepoint, but has not withdrawn consent. Such patients will not contribute data to any of the assessed outcomes.

Partial loss to follow-up is defined as a participant contributing some follow-up data, but no further information is known on other follow-up outcomes. Such participants will contribute to the outcomes for which there are data.

Withdrawals

If a participant prospectively withdraws consent, no further data are captured or retained on or after the date of withdrawal of consent. Depending on when the consent is withdrawn, the above rules on loss to follow-up apply.

Post-randomisation exclusions

If a participant is excluded from the trial, then their data will be excluded from analyses and will not contribute to any of the assessed outcomes.

Imputation

Imputation of missing baseline data (collected prior to randomisation) will be undertaken in order to reduce bias. Although no imputation of missing participant-level outcome data will be carried out in the main analysis of the primary outcome, imputation of instruments (e.g. POP-SS) will be undertaken at item-level according to the rules of the specific instrument.

Sensitivity analyses

It is recommended that sensitivity analyses are carried out where there are missing outcome data[3]. For the primary outcome POP-SS at data 12 months we will explore the explore the impact of missing data on the complete-case treatment estimates and confidence intervals by using multiple imputation and pattern mixture modelling methods depending on level and patterns of missing data.

Statistical Methods

General Methods

The statistical analysis of the RCTs will be based on all women as randomised, irrespective of subsequent compliance with the treatment allocated (intention to treat). The principal comparisons will be:

- In women having a primary prolapse repair,
    - a standard anterior and/or posterior repair will be compared with a standard repair using a biological graft inlay; and
    - a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay.
- In women having a secondary prolapse repair,
    - a standard anterior and/or posterior repair will be compared with a standard repair using a non-absorbable or combined mesh inlay; and
    - a standard anterior and/or posterior repair will be compared with a mesh kit procedure using an introducer device.

The two trials are being considered independently because different surgical options are considered to be appropriate for clinical reasons. Women who are not randomised but who are in the Comprehensive Cohort group will be analysed according to the operation actually carried out.

Descriptive statistics will be tabulated by treatment allocation for all outcomes (mean and SD for continuous data, proportions for binary data). Treatment effects will be estimated with 95% confidence intervals for all outcomes (mean differences for continuous data, odds ratios for binary data). Statistical significance will be at the 5% level and corresponding confidence intervals will be derived. Analyses will be conducted using SAS v9.3.

Primary/Secondary Outcomes

Outcomes at 12 months will be analysed using a generalised linear model which will adjust for minimisation and baseline covariates. The development of treatment effects over time will be explored using repeated measures mixed effects models that make use of available outcome data at each time point, e.g. 6, 12 and 24 months for the POP-SS (this assumes outcome data missing at random conditional on the observed covariates).

Furthermore, it is anticipated that many women may be asymptomatic one year after surgery and their POP-SS will be zero. A composite binary/linear model will be used to analyse the primary outcome (POP-SS at 12 months) so that a distribution of POP-SS with a high proportion of zero values is taken into account. The binary element will be based on a POP-SS=0, and the linear element will treat the POP-SS score as a continuous measure with possible values ranging from 0 to 28.

The menu design of the trials will be taken into account in the analyses of all outcomes. Both RCTs have 3 strata, as shown in Table 2 and Table 3.

Table 2: Number of participants randomised to each stratum in the primary RCT

Stratum	Standard repair (A)	Synthetic mesh (B)	Biological mesh (C)
RCT1	253	256	255
RCT1B	178	181	n/a
RCT1C	116	n/a	114

Table 3: Number of participants randomised to each stratum in the secondary RCT

Stratum	Standard repair (A)	Synthetic mesh (B)	Mesh kit (C)
RCT2	24	24	44
RCT2B	31	28	n/a
RCT2D	1	n/a	3

In the primary RCT, RCT1 will be analysed on its own and treatment effects for treatments B and C (compared with A) will be estimated. In addition, the RCT1 and RCT1B strata will be combined (using just data in arms A and B) in a separate model to create a further estimate of the treatment effect between A and B. Similarly, the RCT1 and RCT1C strata will be combined (using just data in arms A and C) in a separate model to create a further estimate of the treatment effect between A and C. Where strata are combined, the stratum variable will be fitted as a fixed effect in the model. The secondary trial will be similarly analysed, although RCT2 will not be combined with RCT2D due to the small number randomised to RCT2D.

Secondary outcomes will be analysed in a similar fashion to the primary outcome using appropriate link functions.

Subgroup analyses

Subgroup analyses (separately for the two populations) will explore the effect on prolapse symptoms at 12 months after surgery of:

- mesh kit versus other procedures in those that could have been randomised to mesh kits
- concomitant continence procedure or not
- concomitant hysterectomy/cervical amputation/vault procedure or not
- age (<60 or >=60 years)

- parity
- between those having one type of prolapse repair alone (anterior or posterior) versus both

Heterogeneity of treatment effects amongst subgroups will be tested for using the appropriate subgroup by treatment group interactions. Stricter levels of statistical significance (2P<0.01) will be sought, reflecting the exploratory nature of these analyses.

Non-compliance will allocated treatment

The primary analysis strategy of the trial will follow the intention-to-treat principle, i.e. participants will analysed as randomised, regardless of the intervention received. However, secondary analyses may be undertaken to investigate issues relating to compliance (e.g. mesh inlays being misidentified as mesh kits). Depending on levels and patterns of non-compliance analyses methods other than intention-to-treat may be used, for example per-protocol analyses or estimation of complier average treatment effects.

Methodological analyses

The responses from women and their objective clinical findings will provide a rich data source for exploration of the correlation between patient-reported and clinician-observed outcomes, and between prolapse symptoms and their effect on quality of life. This methodological research is intended to advance the controversial field.

1.1. Timing of analyses

An analysis of 12 month outcomes (including the primary outcome) will be performed and published one year after recruitment closes. A final analysis of all outcomes will be conducted at the end of the trial when all follow-up has been completed (up to 24 months).

Sample Size and Power Calculation

In an average population of women having prolapse surgery, about 70% will be having a primary procedure. Two comparisons will be made:

- a standard repair versus a standard repair using a biological graft inlay; and
- a standard repair versus a standard repair using a non-absorbable or combined mesh inlay.

Pilot data have shown that a conservative estimate of the standard deviation of the primary patient-reported outcome POP-SS is 8 units. A difference in means of 2 units would represent an improvement in the response to a POP-SS question, for example, a feeling of something coming down or in the vagina, from 'Most of the Time' to 'Occasionally'. To detect a standardised difference of 0.25 with 90% power and alpha equal to 0.025 (to maintain the nominal p value at 0.05 with two tests being used), we would need to randomise 400 women to each arm of the study. Best efforts using evidence based techniques will be employed to maximise the response rate at follow up. Nevertheless, we feel it prudent to inflate the estimated sample size for 15% dropout at one year requiring approximately 1450 women having primary surgery to be recruited to the trial. Adjusting for baseline covariates and minimising the loss to follow up will potentially improve this power. A trial of this size would also be adequately powered to detect important differences in the economic and secondary outcomes.

It is estimated that the other 30% of women requiring anterior and/or posterior repair will receive a secondary or subsequent repair. Therefore, during the proposed time period required for recruiting 1450 women to the primary repair RCT above, it is anticipated approximately 620 women having secondary surgery will be eligible and will be willing to be randomised. Within the secondary RCT two comparisons will be made:

- a standard repair versus a standard repair using a non-absorbable or combined mesh inlay; and

- a standard repair versus a mesh kit procedure.

It would be possible to detect with 90% power and alpha equal to 0.025 a standardised effect size of 0.38 which equates to 3 points on the POP-SS scale (this estimated effect detectable has been calculated adjusting for potential 15% dropout at one year). The pilot data from IMPRESS indicated that women having secondary repairs have a higher level of symptoms at baseline. Therefore it is biologically plausible that these women may show a larger benefit from the options available.

Thus 2070 women will be randomised in total. Based on data from the feasibility study, we expect that in a typical centre, 200 women a year will be eligible, of whom 50% will be willing to be randomised. Of these women, 70% will be having primary surgery, 30% will have both anterior and posterior surgery, 15% may have a concomitant continence procedure and 30% a concomitant upper vaginal procedure (e.g. cervical amputation or vaginal hysterectomy). More than 15 centres are willing to take part.

If we conservatively assume 50% of the women will agree to be randomised, we calculate we will need the equivalent of 18 months full time recruitment to randomise 2070 women and will follow up 4140 women in total including those in the Comprehensive Cohort. Allowing for about another 10% who will not wish to be studied in any way, we will need to approach around 4500 women.

References

1 Hagen S, Glazener C, Sinclair L, Stark D, Bugge C. Psychometric properties of the pelvic organ prolapse symptom score. BJOG: an International Journal of Obstetrics & Gynaecology 2009; 116(1):25-31.

2 The EuroQoL - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199−208.

3 White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analyses in randomised trials with missing outcome data. British Medical Journal, 2011; 342: d40.

Appendix 6 Health economics

Cost of anaesthesia drugs

Anaesthesia type	Drug	Unit price (£)	Price per:	Resource use	Cost per average case (£)	Comments	Sources
General	Propofol, 1% injection	4.18	20-ml ampoule	1 ampoule	4.18	One ampoule will be sufficient for a standard case; Dr Karen Cranfield	BNF;[34] personal communication
	Fentanyl, 100 µg	0.45	2-ml ampoule (50 µg/ml)	1 ampoule	0.45	One ampoule is sufficient to treat an average cost; Dr Karen Cranfield	
	Morphine	0.72	1-ml vial	1 vial	0.72	For pain relief; Dr Karen Cranfield	
	Sevoflurane (volatile agent)	123	250-ml bottle	25 ml	12.30	Baxter UK, Berkshire, 2013	www.baxterhealthcare.co.uk/downloads/prescribing_information/hospital_products/anaesthesia_critical_care/sevoflurane_pi.pdf
	Laryngeal mask	29.50	Box of 10	1	2.95	Pro-act medical; laryngeal airway disposable pre-breathe; Dr Karen Cranfield	Pro-act medical; personal communication
Total cost: general anaesthesia					*20.60*	*Anaesthesia consumables cost per average case*	
Spinal	Bupivacaine hydrochloride anhydrous injection (0.5%)	1.45	4-ml ampoule	1 ampoule	*1.45*	Resource-use requirements provided by Dr Karen Cranfield	BNF;[34] personal communication
	Lidocaine	0.40	10-ml ampoule	1 ampoule	*0.40*		
Total cost: spinal anaesthesia					*1.85*	*Anaesthesia consumables cost per average case*	
Local	Lidocaine	0.40	10-ml ampoule	1 ampoule	0.40	Resource-use requirements provided by Dr Karen Cranfield	BNF;[34] personal communication
Total cost: local anaesthesia					*0.40*		

No differences in anaesthesia cost reported across trial arms. Assumed that unit costs of each individual type of anaesthesia are the same across randomised arms.

Other surgical drugs

Anaesthesia type	Drug	Unit price (£)	Price per:	Resource use	Cost per average case (£)	Comments	Sources
General/spinal	Cyclizine lactate injection (50 mg/ml)	0.65	1-ml ampoule	1 ampoule	*0.65*	Resource-use requirements provided by Dr Karen Cranfield	BNF;[34] personal communication
	Dexamethasone, injection	4.80	2-ml vial	1 vial	*4.80*		
	Ondansetron injection (2 mg/ml)	1.00	2-ml ampoule	1 ampoule	*1.00*		
Total: other surgical drugs					*6.45*		

Assume additional drugs outlined are for patients receiving general and spinal anaesthesia only. No further drugs required for local anaesthesia.

Absorbent pads for the leakage of urine

Pads	Number per day	Number per night	Number of days/nights[39]	Total number of pads (day)	Price (2005)	Price (£) per day pad 2005	Price (£) per day pad 2014	Total number of pads (night)	Price 2005	Per night pad 2005	Per night pad 2014	Notes/sources
Washable pads	3	1	30	90	9	9/90 = £0.10	0.10/232.3 × 290.5 = *0.13*	30	6	6/30 = £0.20	0.20/232.3 × 290.5 = *0.25*	Fader 2008,[39] HCHS inflation index (PSSRU)
Pull-up pads	3	1	30	90	78.70	78.70/90 = 0.87	0.87/232.3 × 290.5 = *1.09*	30	25.50	25.50/30 = 0.85	0.85/232.3 × 290.5 = *1.06*	
Average cost							*0.61*				*0.66*	

Note that the actual participant-level cost in the analysis depends on the reported amount and frequency of leakage.
Calculations assume an equal split between washable and pull-up pads.
The shading relates to the result of the calculation: the values in row 'Average cost' are used in the analysis.

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Answer to question on leakage	Number of times pass per day	Number of pads required (day)	Unit cost (£) of day pad	Total cost (£) of day pad per year	Number of pads (night)	Unit cost (£) of night pad	Total cost (£) of night pad per year	Total cost (£) of pads
Not answered/never		1	0.61	0.61 × 1 × 365 = £222.65	1	0.66	0.66 × 1 × 365 = £240.90	463.55
Once weekly or less often		1+ (1/week)	0.61	222.65 + (1 × 52 × 0.61) = 254.37	1	0.66	£240.90	495.27
Two to three times per week		1+ (3/week)	0.61	222.65 + (3 × 52 × 0.61) = 317.81	1	0.66	£240.90	558.71
Daily		2	0.61	222.65 × 2 = 445.30	1	0.66	£240.90	686.20
Several times/day		4	0.61	222.65 × 4 = 890.60	1	0.66	£240.90	1131.50
All of the time	1–6 or missing	6	0.61	222.65 × 6 = 1335.90	2	0.66	481.80	1817.70
	7–8: 8	9	0.61	222.65 × 9 = 2003.85	2	0.66	481.80	2485.65
	9–10: 10	11	0.61	222.65 × 11 = 2449.15	2	0.66	481.80	2930.93
	11–12: 12	13	0.61	222.65 × 13 = 2894.45	2	0.66	481.80	3376.25
	13+: 14	15	0.61	222.65 × 15 = 3339.75	2	0.66	481.80	3821.55

Indwelling catheter/permanent catheter unit cost

Requirement	Product	Manufacturer	Pack size	Number of packs required for 1 year of treatment	Unit cost (£), 2015 tariff	Total cost (£)	Reference/notes
Sterile catheterisation insertion pack	Cath-it® (1 pack)	Richardson Healthcare, Hertfordshire, UK	1	4	10.95	43.80	NHS EDT April 2015
Sterile lubricant for instillation	Optilube® sterile lubricating jelly (1 × 11-ml syringe)	Optimum Medical, Leeds, UK	1	4	1.13	4.52	
Indwelling catheter	Folysil® X-tra (size 14), pack size 1	Coloplast, Peterborough, UK	1	6 (four, plus two spares)	6.25	37.50	
Leg bags (assumes patients have continuous drainage)	Simpla® profile, 500 ml, 25-cm tube	Coloplast	10	6	29.26	175.56	
Catheter stabilisation device	Leg bag holder – aqua sleeve, size standard	Coloplast	4	2	8.33	16.66	
Night drainage bags	Single use, Prosys® leg drainage bags (2 l)	CliniSupplies, London, UK	10	37	3.04	112.48	
Total						*390.52*	

EDT, Electronic Drug Tariff.

Notes

Assume use over 12 weeks.
Assume continuous drainage rather than valve usage as per e-mail from CG.
Assume leg bag is changed once per week: 52 weeks per year, pack size 10, requires 52/10 (rounded gives six packs per year).
Stabilisation device: ordering information assumes reorder of one box every 6 months; two boxes of four required to cover 1 year.
Single-use night drainage bags.
Assume no catheter maintenance solutions required.

Intermittent/disposable or reusable catheters (assume three per day)

Product	Manufacturer	Pack size	Number of packs required for 1 year	Unit cost (£, 2015)	Total cost (£)	Reference/notes
HiSlip plus®	CS Bullen Healthcare Ltd, Liverpool, UK	30	37	32.55	1204.35	
Advance Plus intermittent catheter	Hollister, Libertyville, IL, USA	25	44	69.02	3036.88	
SpeediCath® compact	Coloplast	30	37	45.85	1696.45	
SpeediCath	Coloplast	30	37	44.28	1638.36	
Hydrosil	Rochester Medical (acquired by Bard Medical), Sussex, UK	30	37	43.19	1598.03	
LoFric® Sense™	Wellspect Healthcare, Stonehouse, UK	30	37	46.62	1724.94	
Average cost for a full year of treatment					*1816.50*	

Assuming that all patients are using disposable catheters, as these are preferred for hygiene reasons.

Accident and emergency unit costs for use in the analysis

Code	Description	HRG	HRG description	Number of attendances	National average (£)	Lower quartile (£)	Upper quartile (£)	No. of data submissions
T01NA	Type 01 Non-Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	3,262,747	103	84	121	139

HRG, Healthcare Resource Group.

Costing of urodynamics

OPCS code	HRG	HRG description	Assumed category	Assumed discipline	National average unit cost (£, 2013–14)	Lower quartile (£)	Upper quartile (£)
M474	LB42 -A	Dynamic studies of urinary tract; age 19+	Outpatients	Gynaecology	186	129	209
U264	LB42 -A						
For use in analysis					*186*	*129*	*209*

HRG, Healthcare Resource Group.
Assumes all urodynamics investigations for these patients will take place in Urology outpatient clinics.

Costing of ultrasound

OPCS code:	OPCS description	HRG	HRG description	Assumed category	Assumed discipline	National average unit cost (£, 2013–14)	Lower quartile (£)	Upper quartile (£)
M497	High intensity focused ultrasound of bladder	LB49 – flag a	High-intensity focused ultrasound	Outpatient	Gynaecology	166	170	170
Q555	Transvaginal ultrasound examination of female genital tract	MA23	Lower genital tract, minor procedures, category 2	Outpatient	Gynaecology	160	123	191
U216	Ultrasound scan NEC	RA23	Ultrasound scan < 20 minutes	Diagnostic imaging – outpatient	Outpatient	52	38	62
For use in analysis:						*52*	*38*	*62*

HRG, Healthcare Resource Group; OPCS, operating procedure codes.
Assumes all urodynamics investigations for these patients will take place in Urology outpatient clinics.

Costs of resource use seeing health professionals

Expert seen	Unit cost (£)	Unit cost (£), including qualification costs	Per:	Average length per case	Cost per case (£), including qualification costs	Sources/notes
Community pharmacist	128	142	Hour of direct clinical activities	0.25	32 (35.50)	PSSRU 2014; section 9.6 – community pharmacist; no average time given (assume 15 minutes)

Costs of repeat prolapse surgery

OPCS code	OPCS description	HRG	HRG description	Assumed category	Assumed discipline	National average unit cost (£, 2013–14)	Lower quartile (£)	Upper quartile (£)	Weight	National average unit cost (2013–14)	Lower quartile (£)	Upper quartile (£)
P232/P233/	Anterior/posterior colporrhaphy NEC	MA04D	Lower genital tract – intermediate open procedure (cc score (0–2)	Elective inpatient	N/A	2187	1656	2340	0.5	1093.50	828	1170
P236/P237/P247	Colporrhaphy with mesh reinforcement/ sacrospinous fixation	MA03D	Lower genital tract – major open procedure (cc score 0–2)	Elective inpatient	N/A	2475	2075	2766	0.5	1237.50	1037.50	1383
For use in analysis:										*2331*	*1865.50*	*2553*

cc, complications and comorbidities; HRG, Healthcare Resource Group; N/A, not applicable; NEC, not elsewhere classifiable.
Currently assumes that 50% will get mesh reinforcement, 50% will get a standard repair without mesh reinforcement.

Costs of incontinence surgical procedure (total vaginal length – transobturator tape)

OPCS code	OPCS description	HRG	HRG description	Assumed category	Assumed discipline	National average unit cost (£, 2013–14)	Lower quartile (£)	Upper quartile (£)	Weight	National average unit cost (£, 2013–14)	Lower quartile (£)	Upper quartile (£)
M533/M536	Introduction of TVT/TOT	LB51 (B)	Vaginal tape operations for UI_ (CC 0–1)	Elective inpatient	N/A	1586	1293	1850	0.483	766.04	624.52	893.55
M533/M536	Introduction of TVT/TOT	LB51 (B)	Vaginal tape operations for UI_ (CC 0–	Day-case procedure	N/A	1173	951	1354	0.517	606.44	491.67	700.02
For use in analysis				*Weighted average*						*1372.48*	*1116.19*	*1593.57*

HRG, Healthcare Resource Group; N/A, not applicable; TOT, transobturator tape.
Weight (elective), 3684/7625 = 0.483; weight day case, 3941/7625 = 0.517, is determined by number of cases reported in the reference cost tables for HRG code LB51B apportioned between elective inpatient and day-case procedures. It is assumed that all incontinence procedures reported will be LB51 (B) meaning 0-1 CC.

Costs of readmissions to hospital

OPCS code	OPCS description	HRG	HRG description	Category	Assumed discipline	National average unit cost (£, 2013 –14)	Lower quartile (£)	Upper quartile (£)	Weight	Average cost (£)	Lower quartile (£)	Upper quartile (£)
P209	Unspecified extirpation of lesion of vagina	MA23	Minimal lower genital tract procedures	Elective inpatient	N/A	1062	731	1369	0.072	76.46	52.63	98.57
P261	Insertion of Hodge pessary into vagina	MA23	Minimal lower genital tract procedures	Day case	N/A	733	461	940	0.584	428.07	269.22	548.96
P271	Evacuation of haematoma from vagina	MA22	Minor lower genital tract procedures	Elective inpatient	N/A	1416	1131	1722	0.051	72.22	57.68	87.82
P292	Colpotomy NEC	MA22	Minor lower genital tract procedures	Day case	N/A	945	767	1078	0.293	276.89	224.73	315.85
For use in analysis (weighting of all)										*853.64*	*604.26*	*1051.2*
Day-case weighting										*803.81*	*563.21*	*986.09*
Elective inpatient weighting										*1207.85*	*£895.80*	*1514.43*

FCE, finished consultant episode; HRG, Healthcare Resource Group; N/A, not applicable.

Notes

MA22, elective inpatient $N = 1504$; day case $N = 8736$; MA23, elective inpatient $N = 2145$; day case $N = 17,384$.

Averages based on weighted by FCE for two HRG codes, weighted by elective inpatient and day-case procedures.

For cases for which we know it was a day-case procedure (i.e. no. nights admitted = 0), we use day-case weighting by HRG code.

For cases for which there was > 0 nights reported, then we use the elective inpatient admitted tariff weighting by HRG code.

Costs for a ring pessary

Product	Price (£) for 1
Bioteque America (San Jose, CA, USA)	20.00
GBUK Healthcare (Selby, UK)	19.00
Milex (Mediplus, High Wycombe, UK)	20.94
Average	*19.98*

Costs for a shelf pessary (assume Gellhorn pessary)

Product	Price (£) for 1
Bioteque America	21.50
GBUK	20.49
Milex	22.55
Average	*21.51*

Appendix 7 Evidence synthesis

Meta-analyses: prolapse surgery with no mesh compared with prolapse surgery with mesh (Fiona Stewart, Lynda Constable, Moira Cruickshank, Clare Robertson)

This appendix contains the results of meta-analyses of RCTs comparing prolapse surgery with and without mesh, updated with new RCTs published since the last Cochrane review in 2013[18] and with the new data from PROSPECT.

Meta-analyses have been undertaken for outcomes measured up to 1 year after surgery and for the same outcomes measured beyond the first postoperative year (usually for 2 years, with some trials following up participants for 3 years).

Within 1 year of surgery, the risk of having persistent prolapse symptoms is significantly greater for women who are undergoing surgery with mesh kit than for those without mesh (RR 0.73, 95% CI 0.59 to 0.90). There is no evidence of a difference between surgery without mesh and surgery with absorbable, biological graft or non-absorbable mesh (*Figure 35*). PROSPECT has contributed over half of the evidence for the graft and mesh inlay outcomes.

References

No mesh compared with absorbable mesh

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Robert M, Girard I, Brennand E, Tang S, Birch C, Murphy M, *et al.* Absorbable mesh augmentation compared with no mesh for anterior prolapse: a randomized controlled trial. *Obstet Gynecol* 2014;**123**:288–94.[67]

No mesh compared with biological graft

Gandhi S, Goldberg RP, Kwon C, Koduri S, Beaumont JL, Abramov Y, *et al.* A prospective randomized trial using solvent dehydrated fascia lata for the prevention of recurrent anterior vaginal wall prolapse. *Am J Obstet Gynecol* 2005;**192**:1649–54.[68]

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Hviid U, Hviid TV, Rudnicki M. Porcine skin collagen implants for anterior vaginal wall prolapse: a randomised prospective controlled study. *Int Urogynecol J* 2010;**21**:529–34.[69]

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Sung VW, Rardin CR, Raker CA, Lasala CA, Myers DL. Porcine subintestinal submucosal graft augmentation for rectocele repair: a randomized controlled trial. *Obstet Gynecol* 2012;**119**:125–33.[71]

Study or subgroup	No mesh Events	Total	Mesh Events	Total	Weight	RR M–H, fixed, 95% CI
No mesh vs. absorbable mesh						
Allahdin 2008[66]	25	34	27	32	81.7%	0.87 (0.68 to 1.12)
Robert 2014[67]	11	29	6	27	18.3%	1.71 (0.73 to 3.98)
Subtotal (95% CI)		**63**		**59**	**100.0%**	**1.02 (0.78 to 1.35)**
Total events	36		33			
Heterogeneity: $\chi^2 = 2.99$, df = 1 ($p = 0.08$); $I^2 = 67\%$						
Test for overall effect: $z = 0.17$ ($p = 0.87$)						
No mesh vs. biological graft						
Gandhi 2005[68]	6	57	6	55	3.8%	0.96 (0.33 to 2.81)
Glazener Primary 2016	117	342	140	337	88.6%	0.82 (0.68 to 1.00)
Hviid 2010[69]	1	26	1	28	0.6%	1.08 (0.07 to 16.35)
Meschia 2007[70]	13	103	9	98	5.8%	1.37 (0.62 to 3.07)
Sung 2012[71]	4	58	2	64	1.2%	2.21 (0.42 to 11.60)
Subtotal (95% CI)		**586**		**582**	**100.0%**	**0.88 (0.73 to 1.06)**
Total events	141		158			
Heterogeneity: $\chi^2 = 2.85$, df = 4 ($p = 0.58$); $I^2 = 0\%$						
Test for overall effect: $z = 1.37$ ($p = 0.17$)						
No mesh vs. non-absorbable mesh						
Carey 2009[72]	7	62	3	61	1.6%	2.30 (0.62 to 8.47)
De Tayrac 2013[73]	35	67	21	66	11.5%	1.64 (1.08 to 2.50)
El-Nazer 2012[74]	6	19	1	18	0.6%	5.68 (0.76 to 42.70)
Glazener Primary 2016	143	395	138	389	75.5%	1.02 (0.85 to 1.23)
Glazener Secondary 2016	22	49	18	44	10.3%	1.10 (0.68 to 1.76)
Turgal 2013[75]	5	20	1	20	0.5%	5.00 (0.64 to 39.06)
Subtotal (95% CI)		**612**		**598**	**100.0%**	**1.17 (1.00 to 1.37)**
Total events	218		182			
Heterogeneity: $\chi^2 = 9.90$, df = 5 ($p = 0.08$); $I^2 = 49\%$						
Test for overall effect: $z = 1.93$ ($p = 0.05$)						
No mesh vs. mesh kit						
Altman 2011[76]	60	174	107	176	89.4%	0.57 (0.45 to 0.72)
Delroy 2013[77]	10	39	2	40	1.7%	5.13 (1.20 to 21.92)
Glazener Secondary 2016	12	22	16	44	9.0%	1.50 (0.87 to 2.59)
Subtotal (95% CI)		**235**		**260**	**100.0%**	**0.73 (0.59 to 0.90)**
Total events	82		125			
Heterogeneity: $\chi^2 = 17.92$, df = 2 ($p = 0.0001$); $I^2 = 89\%$						
Test for overall effect: $z = 2.99$ ($p = 0.003$)						
Test for subgroup differences: $\chi^2 = 13.79$, df = 3 ($p = 0.003$); $I^2 = 78.3\%$						

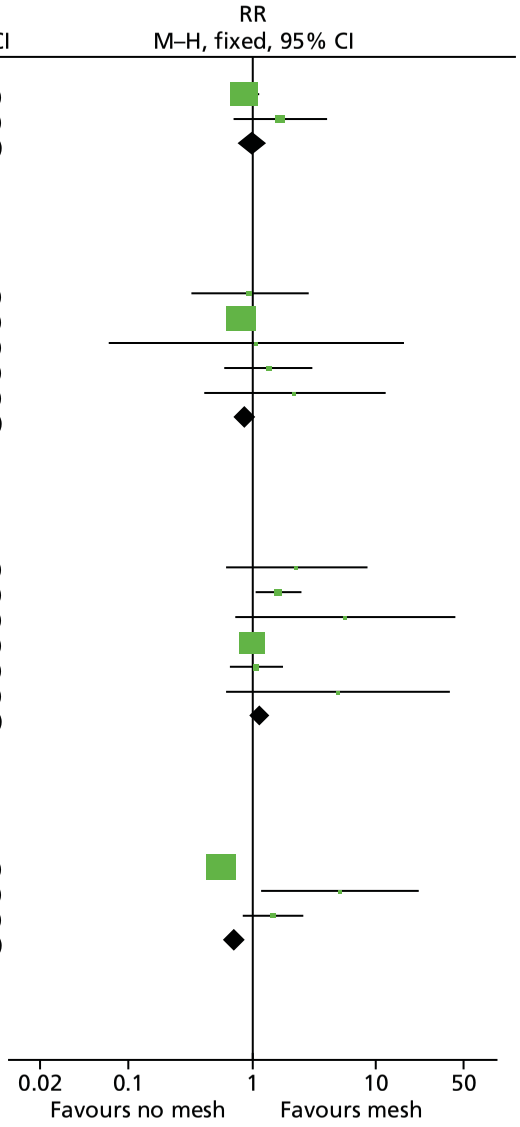

FIGURE 35 Number of women with prolapse symptoms (up to 1 year after surgery). df, degrees of freedom; M-H, Mantel-Haenszel.

No mesh compared with non-absorbable mesh

Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, *et al.* Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. *BJOG* 2009;**116**:1380–6.[72]

De Tayrac R, Cornille A, Eglin G, Guilbaud O, Mansoor A, Alonso S, *et al.* Comparison between trans-obturator trans-vaginal meshand traditional anterior colporrhaphy in the treatmentof anterior vaginal wall prolapse: results of a French RCT. *Int Urogynecol J* 2013;**24**:1651–61.[73]

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No mesh compared with mesh kit

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Glazener 2016, Primary and Secondary – reference is to the current monograph.

Beyond the first postoperative year, the risk of persistent prolapse symptoms is greater with biological graft than surgery without mesh (RR 0.78, 95% CI 0.63 to 0.97). There is no evidence of a difference between surgery without mesh and surgery with absorbable or non-absorbable mesh or mesh kit (*Figure 36*). PROSPECT has contributed over half the evidence for the graft and mesh inlay outcomes.

References

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Allahdin S, Glazener C, Bain C. A randomised controlled trial evaluating the use of polyglactin mesh, polydioxanone and polyglactin sutures for pelvic organ prolapse surgery. *J Obstet Gynaecol* 2008;**28**:427–31.[66]

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No mesh compared with biological graft

Dahlgren E, Kjolhede P, RPOP-PELVICOL Study Group. Long-term outcome of porcine skin graft in surgical treatment of recurrent pelvic organ prolapse. An open randomized controlled multicenter study. *Acta Obstet Gynecol Scand* 2011;**90**:1393–401.[80]

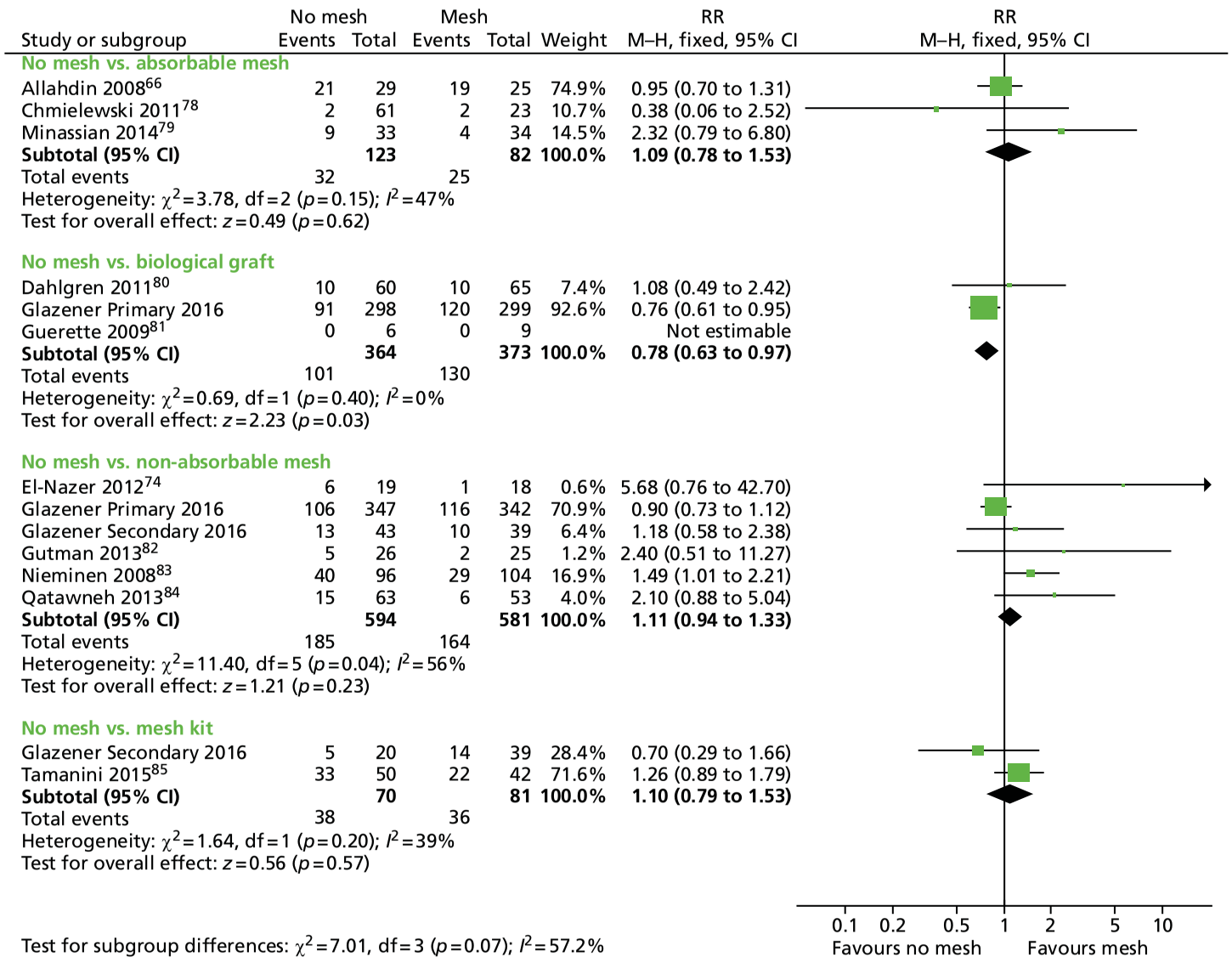

FIGURE 36 Number of women with prolapse symptoms (> 1 year after surgery). df, degrees of freedom; M-H, Mantel-Haenszel.

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No mesh compared with mesh kit

Glazener 2016, Primary and Secondary – reference is to the current monograph.

Tamanini JT, de Oliveira Souza Castro RC, Tamanini JM, Castro RA, Sartori MG, Girão MJ. A prospective, randomized, controlled trial of the treatment of anterior vaginal wall prolapse: medium term follow up. *J Urol* 2015;**193**:1298–304.[85]

Within the first postoperative year, the risk of objective failure is significantly lower for women undergoing surgery with non-absorbable mesh (RR 2.79, 95% CI 1.83 to 4.26) or mesh kit (RR 3.67, 95% CI 2.07 to 6.52). There is no evidence of a difference between surgery without mesh and surgery with absorbable mesh or biological graft (*Figure 37*). PROSPECT has contributed over half of the evidence for the graft and about one-third for the mesh inlay outcomes.

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Allahdin S, Glazener C, Bain C. A randomised controlled trial evaluating the use of polyglactin mesh, polydioxanone and polyglactin sutures for pelvic organ prolapse surgery. *J Obstet Gynaecol* 2008;**28**:427–31.[66]

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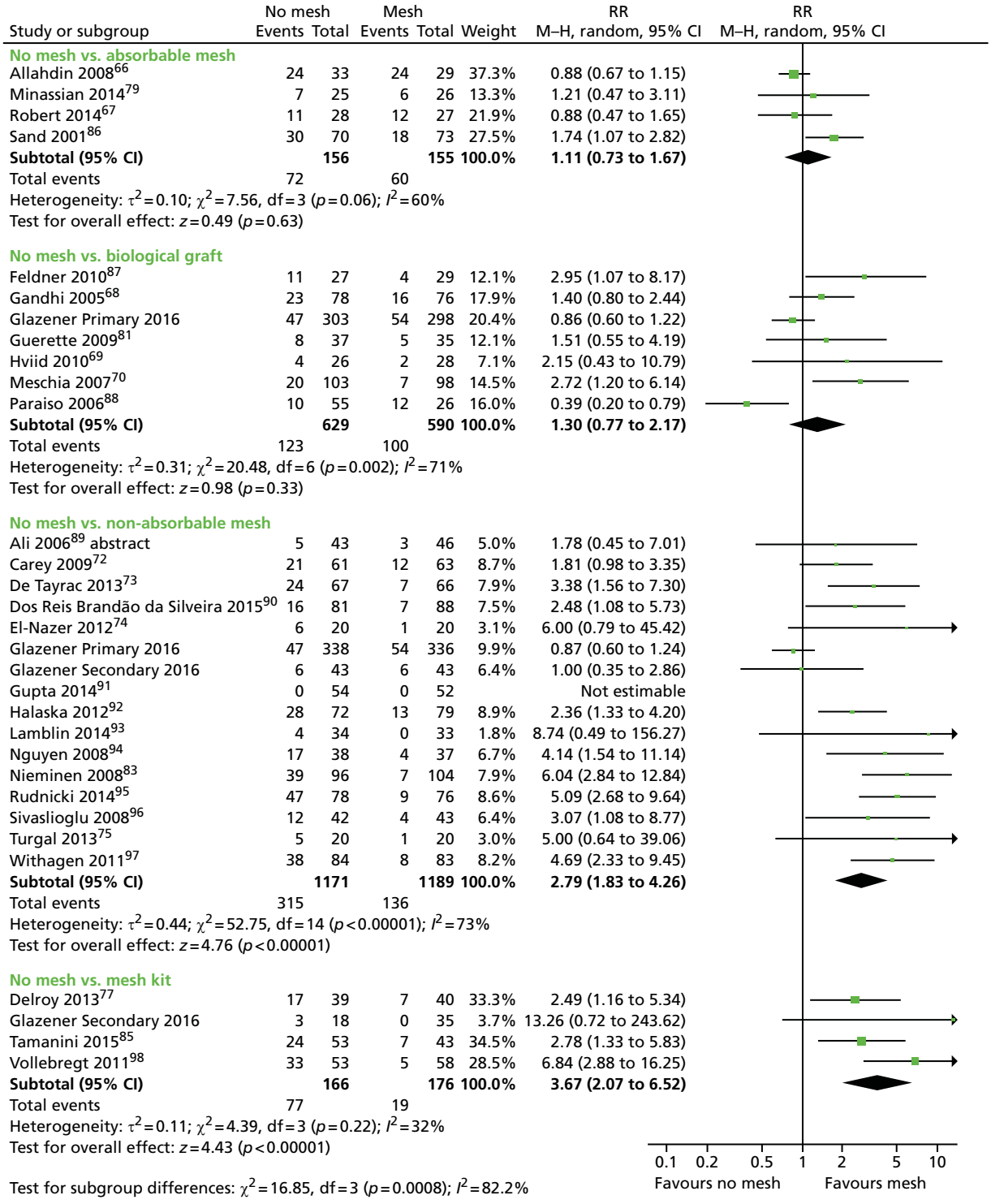

FIGURE 37 Number of women with objective failure (up to 1 year after surgery). df, degrees of freedom; M-H, Mantel-Haenszel.

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Beyond the first postoperative year, the risk of objective failure for women undergoing operations without mesh is greater than for surgery with non-absorbable mesh (RR 2.53, 95% CI 1.52 to 4.22). There is no evidence of a difference between surgery without mesh and surgery with absorbable mesh, biological graft or mesh kit (*Figure 38*). PROSPECT did not measure objective outcomes after the first year.

References

No mesh compared with absorbable mesh

Allahdin S, Glazener C, Bain C. A randomised controlled trial evaluating the use of polyglactin mesh, polydioxanone and polyglactin sutures for pelvic organ prolapse surgery. *J Obstet Gynaecol* 2008;**28**:427–31.[66]

Chmielewski L, Walters MD, Weber AM, Barber MD. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. *Am J Obstet Gynecol* 2011;**205**:69.e1–8.[78]

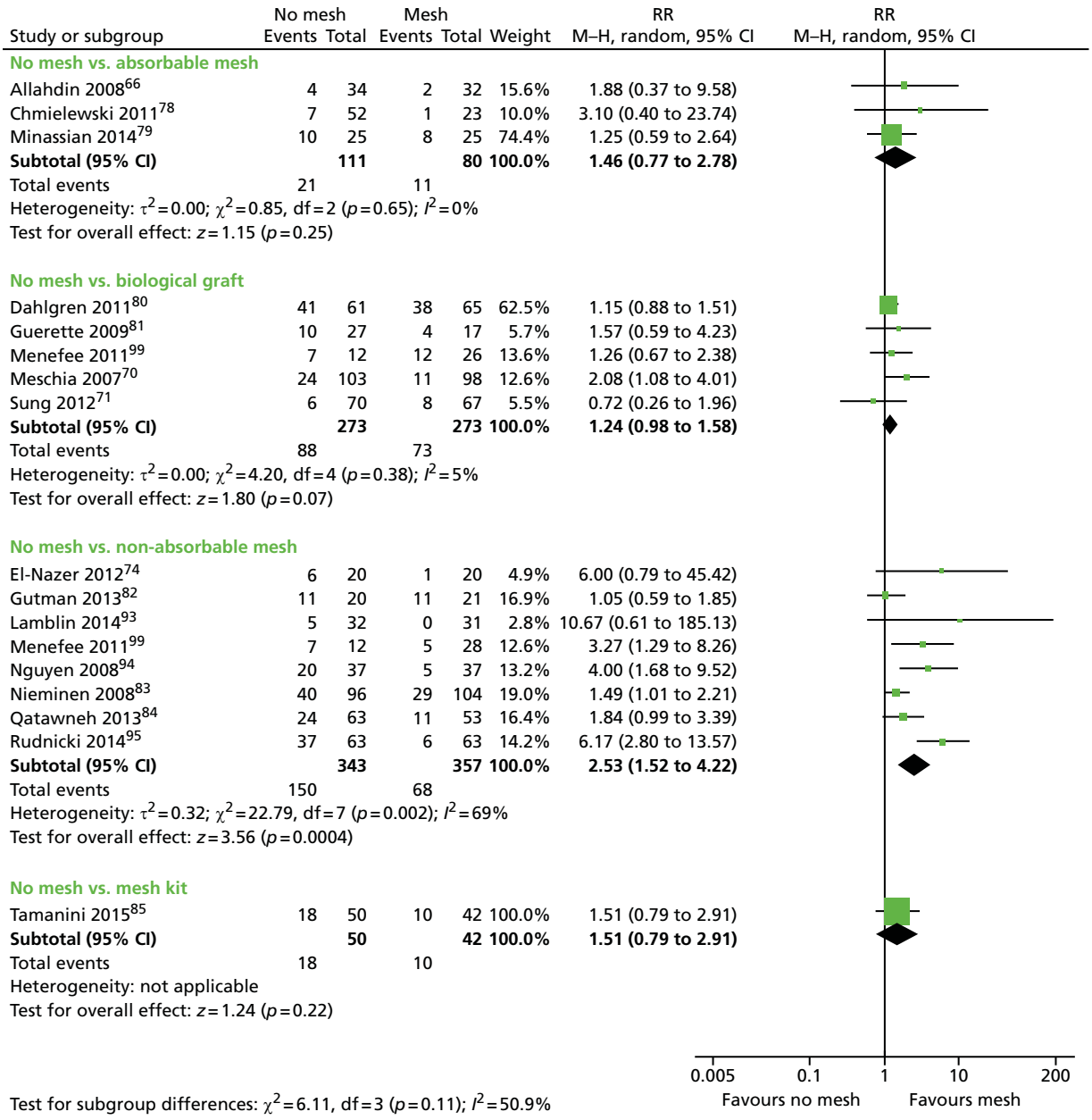

FIGURE 38 Number of women with objective failure (> 1 year after surgery). df, degrees of freedom; M-H, Mantel-Haenszel.

Minassian VA, Parekh M, Poplawsky D, Gorman J, Litzy L. Randomized controlled trial comparing two procedures for anterior vaginal wall prolapse. *Neurourol Urodyn* 2014;**33**:72–7.[79]

No mesh compared with biological graft

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No mesh compared with non-absorbable mesh

El-Nazer MA, Gomaa IA, Ismail Madkour WA, Swidan KH, El-Etriby MA. Anterior colporrhaphy versus repair with mesh for anterior vaginal wall prolapse: a comparative clinical study. *Arch Gynecol Obstet* 2012;**286**:965–72.[74]

Gutman RE, Nosti PA, Sokol AI, Sokol ER, Peterson JL, Wang H, *et al.* Three-year outcomes of vaginal mesh for prolapse: a randomized controlled trial. *Obstet Gynecol* 2013;**122**:770–7.[82]

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Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. *Obstet Gynecol* 2008;**111**:891–8.[94]

Nieminen K, Hiltunen R, Takala T, Heiskanen E, Merikari M, Niemi K, *et al.* Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up. *Am J Obstet Gynecol* 2010;**203**:235.e1–8.[83]

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Rudnicki M, Laurikainen E, Pogosean R, Kinne I, Jakobsson U, Teleman P. Anterior colporrhaphy compared with collagen-coated transvaginal mesh for anterior vaginal wall prolapse: a randomised controlled trial. BJOG 2014;**121**:102–11.[95]

No mesh compared with mesh kit

Tamanini JT, de Oliveira Souza Castro RC, Tamanini JM, Castro RA, Sartori MG, Girão MJ. A prospective, randomized, controlled trial of the treatment of anterior vaginal wall prolapse: medium term followup. *J Urol* 2015;**193**:1298–304.[85]

The risk of requiring further surgery for prolapse is greater for women undergoing surgery with mesh kit than surgery without mesh (RR 3.65, 95% CI 1.51 to 8.86). There is no evidence of a difference between surgery without mesh and surgery with absorbable mesh, biological graft or non-absorbable mesh (*Figure 39*). PROSPECT has contributed well over half the evidence for the graft and about one-third for the mesh inlay outcomes.

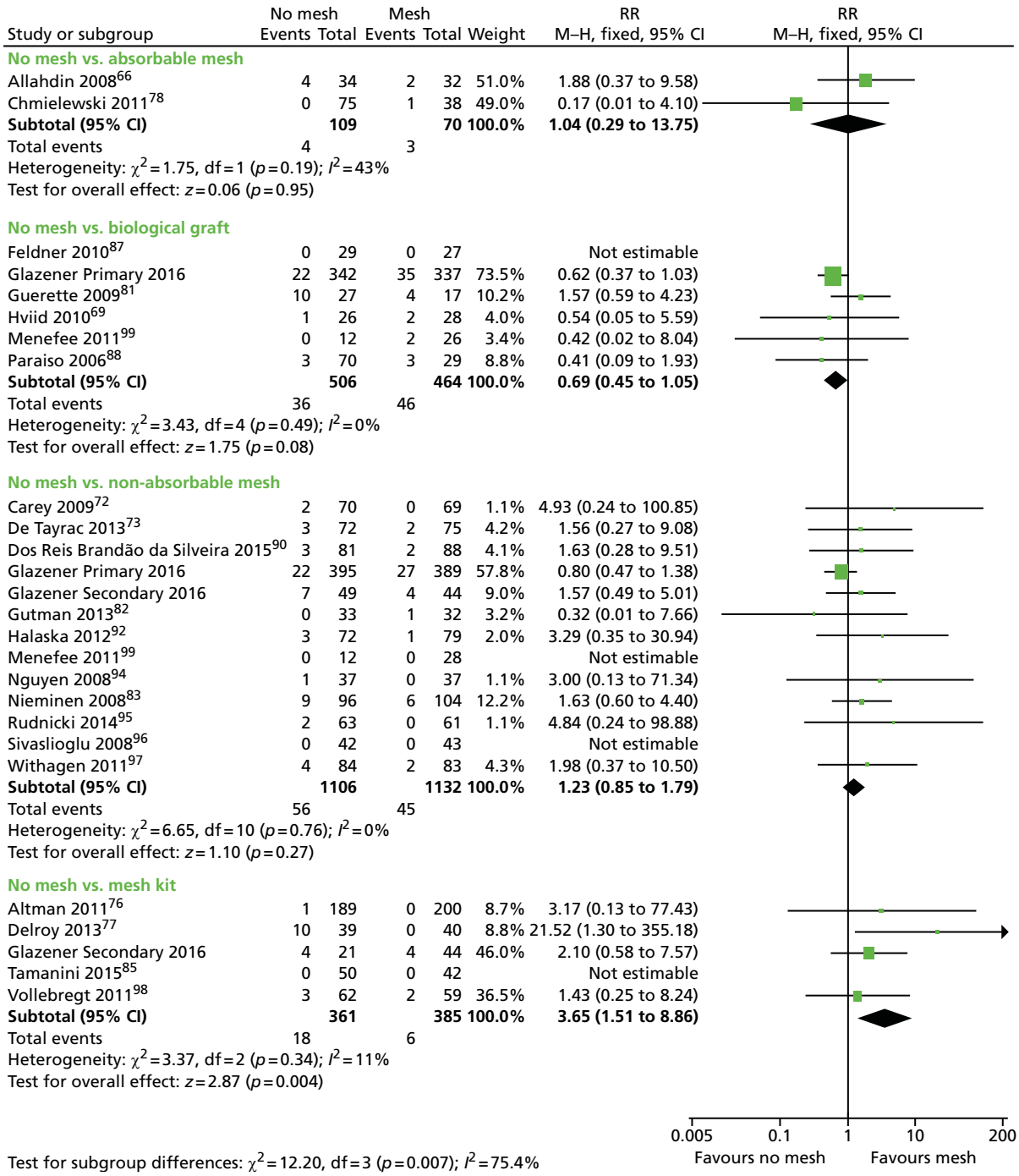

FIGURE 39 Number of women undergoing repeat prolapse surgery. df, degrees of freedom; M-H, Mantel-Haenszel.

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No mesh compared with non-absorbable mesh

Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, *et al.* Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. *BJOG* 2009;**116**:1380–6.[72]

De Tayrac R, Cornille A, Eglin G, Guilbaud O, Mansoor A, Alonso S, *et al.* Comparison between trans-obturator trans-vaginal meshand traditional anterior colporrhaphy in the treatmentof anterior vaginal wall prolapse: results of a French RCT. *Int Urogynecol J* 2013;**24**:1651–61.[73]

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No mesh compared with mesh kit

Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. *N Engl J Med* 2011;**364**:1826–36.[76]

Delroy CA, Castro RDA, Dias MM, Feldner Jr PC, Bortolini MAT, Girao MJBC, *et al.* The use of transvaginal synthetic mesh for anterior vaginal wall prolapse repair: a randomized controlled trial. *Int Urogynecol J* 2013;**24**:1899–907.[77]

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Vollebregt A, Fischer K, Gietelink D, van der Vaart CH. Primary surgical repair of anterior vaginal prolapse: a randomised trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh. *BJOG* 2011;**118**:1518–27.[98]

There is no evidence of a difference between surgery without mesh and surgery with biological graft, non-absorbable mesh or mesh kit in terms of the risk of requiring surgery for UI (*Figure 40*). PROSPECT has contributed almost all of the evidence for the graft and nearly a half for the mesh inlay outcomes.

References

No mesh compared with biological graft

Glazener 2016, Primary and Secondary – reference is to the current monograph.

Menefee SA, Dyer KY, Lukacz ES, Simsiman AJ, Luber KM, Nguyen JN. Colporrhaphy compared with mesh or graft-reinforced vaginal paravaginal repair for anterior vaginal wall prolapse: a randomized controlled trial. *Obstet Gynecol* 2011;**118**:1337–44.[99]

No mesh compared with non-absorbable mesh

De Tayrac R, Cornille A, Eglin G, Guilbaud O, Mansoor A, Alonso S, *et al.* Comparison between trans-obturator trans-vaginal meshand traditional anterior colporrhaphy in the treatmentof anterior vaginal wall prolapse: results of a French RCT. *Int Urogynecol J* 2013;**24**:1651–61.[73]

Dos Reis Brandão da Silveira S, Haddad JM, de Jármy-Di Bella ZI, Nastri F, Kawabata MG, da Silva Carramão S, *et al.* Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. *Int Urogynecol J* 2015;**26**:335–42.[90]

Glazener 2016, Primary and Secondary – reference is to the current monograph.

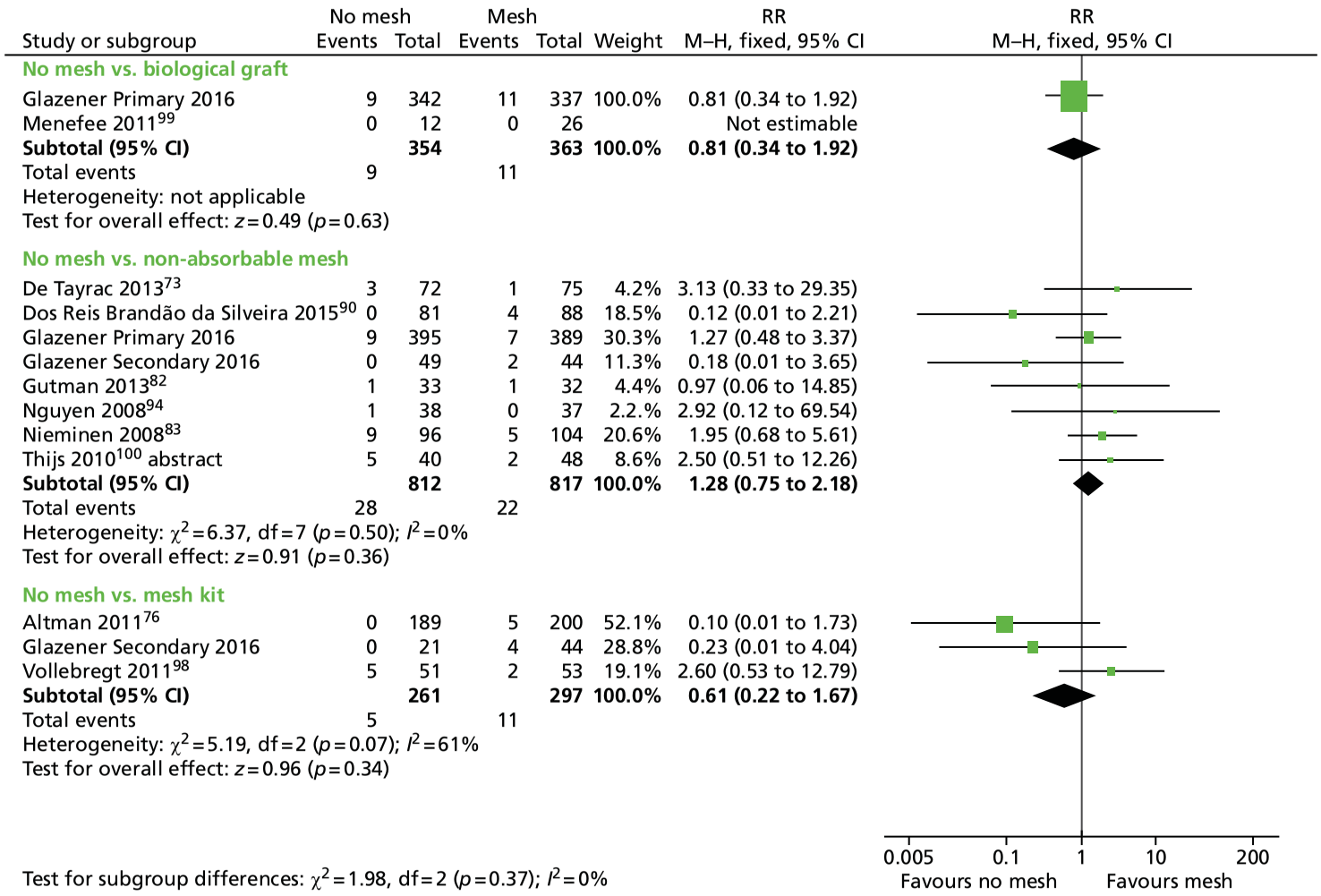

FIGURE 40 Number of women undergoing continence surgery. df, degrees of freedom; M-H, Mantel-Haenszel.

Gutman RE, Nosti PA, Sokol AI, Sokol ER, Peterson JL, Wang H, *et al.* Three-year outcomes of vaginal mesh for prolapse: a randomized controlled trial. *Obstet Gynecol* 2013;**122**:770–7.[82]

Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. *Obstet Gynecol* 2008;**111**:891–8.[94]

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No mesh compared with mesh kit

Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. *N Engl J Med* 2011;**364**:1826–36.[76]

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The risk of requiring surgery for mesh exposure is significantly greater for those undergoing surgery with non-absorbable mesh (RR 0.09, 95% CI 0.05 to 0.17). However, that is expected, as the majority of the women in the no-mesh arms would not have received mesh prolapse surgery, although they might have had mesh for a concomitant operation, such as tape continence surgery or vault suspension. There is no evidence of a difference between surgery without mesh and surgery with biological graft or mesh kit (*Figure 41*).

References

No mesh compared with biological mesh

Glazener 2016, Primary and Secondary – reference is to the current monograph.

Menefee SA, Dyer KY, Lukacz ES, Simsiman AJ, Luber KM, Nguyen JN. Colporrhaphy compared with mesh or graft-reinforced vaginal paravaginal repair for anterior vaginal wall prolapse: a randomized controlled trial. *Obstet Gynecol* 2011;**118**:1337–44.[99]

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No mesh compared with non-absorbable mesh

Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, *et al.* Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. *BJOG* 2009;**116**:1380–6.[72]

Study or subgroup	No mesh Events	Total	Mesh Events	Total	Weight	RR M–H, fixed, 95% CI
No mesh vs. biological graft						
Glazener Primary 2016	2	367	1	368	15.0%	2.01 (0.18 to 22.02)
Menefee 2011[99]	0	12	0	26		Not estimable
Tamanini 2015[85]	0	42	4	50	61.9%	0.13 (0.01 to 2.38)
Vollebregt 2011[98]	0	62	1	59	23.1%	0.32 (0.01 to 7.64)
Subtotal (95% CI)		**483**		**503**	**100.0%**	**0.46 (0.12 to 1.79)**
Total events	2		6			
Heterogeneity: $\chi^2=2.22$, df=2 ($p=0.33$); $I^2=10\%$						
Test for overall effect: $z=1.13$ ($p=0.26$)						
No mesh vs. non-absorbable mesh						
Carey 2009[72]	0	70	3	69	3.4%	0.14 (0.01 to 2.68)
De Tayrac 2013[73]	0	72	4	75	4.3%	0.12 (0.01 to 2.11)
El-Nazer 2012[74]	0	20	1	20	1.5%	0.33 (0.01 to 7.72)
Glazener Primary 2016	2	430	40	435	38.7%	0.05 (0.01 to 0.21)
Glazener Secondary 2016	0	55	4	52	4.5%	0.11 (0.01 to 1.91)
Gutman 2013[82]	0	33	1	32	1.5%	0.32 (0.01 to 7.66)
Halaska 2012[92]	0	72	10	79	9.7%	0.05 (0.00 to 0.87)
Lamblin 2014[93]	0	35	1	33	1.5%	0.31 (0.01 to 7.47)
Menefee 2011[99]	0	12	2	28	1.5%	0.45 (0.02 to 8.65)
Nguyen 2008[94]	0	38	0	37		Not estimable
Nieminen 2008[83]	0	96	8	104	7.9%	0.06 (0.00 to 1.09)
Qatawneh 2013[84]	0	63	4	53	4.7%	0.09 (0.01 to 1.70)
Rudnicki 2014[95]	0	82	7	76	7.6%	0.06 (0.00 to 1.06)
Sivaslioglu 2008[96]	0	42	0	43		Not estimable
Thijs 2010[100] abstract	0	48	4	48	4.4%	0.11 (0.01 to 2.01)
Turgal 2013[75]	0	20	3	20	3.4%	0.14 (0.01 to 2.60)
Withagen 2011[97]	0	84	5	83	5.4%	0.09 (0.01 to 1.60)
Subtotal (95% CI)		**1272**		**1287**	**100.0%**	**0.09 (0.05 to 0.17)**
Total events	2		97			
Heterogeneity: $\chi^2=4.20$, df=14 ($p=0.99$); $I^2=0\%$						
Test for overall effect: $z=7.05$ ($p<0.00001$)						
No mesh vs. mesh kit						
Glazener Secondary 2016	0	25	2	46	35.7%	0.36 (0.02 to 7.25)
Tamanini 2015[85]	0	54	1	43	33.4%	0.27 (0.01 to 6.39)
Vollebregt 2011[98]	0	62	1	59	30.8%	0.32 (0.01 to 7.64)
Subtotal (95% CI)		**141**		**148**	**100.0%**	**0.32 (0.05 to 1.91)**
Total events	0		4			
Heterogeneity: $\chi^2=0.02$, df=2 ($p=0.99$); $I^2=0\%$						
Test for overall effect: $z=1.26$ ($p=0.21$)						
Test for subgroup differences: $\chi^2=5.37$, df=2 ($p=0.07$); $I^2=62.8\%$						

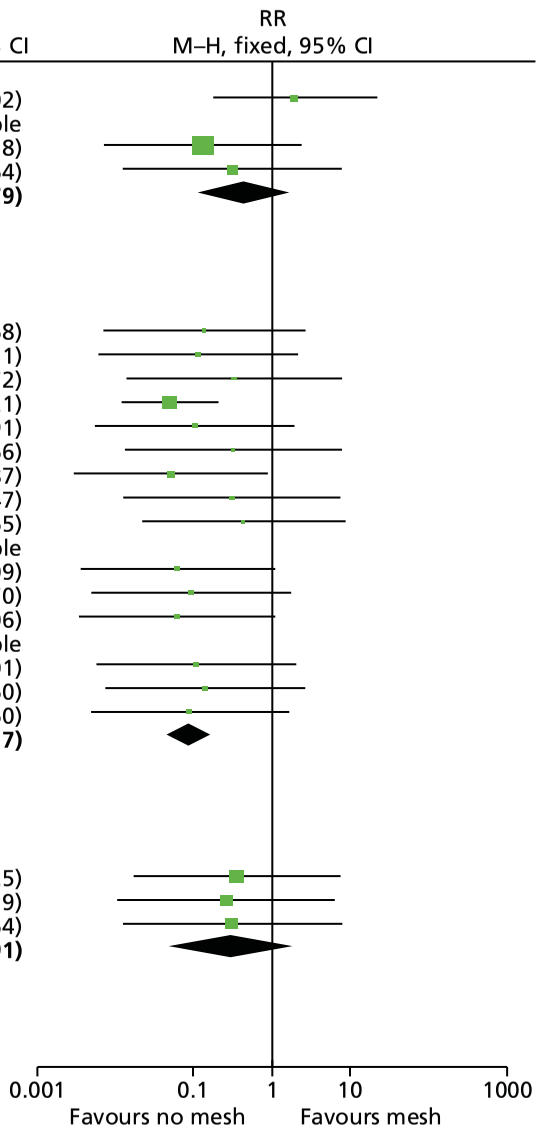

FIGURE 41 Number of women undergoing surgery for mesh exposure. df, degrees of freedom; M-H, Mantel-Haenszel.

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Appendix 8 Mega CONSORT, including comprehensive cohort 3 participants

Type of repair	Primary														
Stratum/comparison	All: 1348			Trial 1: 865		Trial 2:735		RCT1A: 762			RCT1B: 358			RCT1C: 228	
Treatment arm	Standard repair: 545	Synthetic mesh: 435	Biological graft: 368	Standard repair: 430	Synthetic mesh: 435	Standard repair: 367	Biological graft: 368	Standard repair: 252	Synthetic mesh: 255	Biological graft: 255	Standard repair: 178	Synthetic mesh: 180		Standard repair: 115	Biological graft: 113
Received surgery	*537 (99%)*	*425 (98%)*	*363 (99%)*	*425 (99%)*	*425 (98%)*	*359 (98%)*	*363 (99%)*	247	250	251	178	175		112	112
Standard repair	*512 (95%)*	*60 (14%)*	*57 (16%)*	*403 (95%)*	*60 (14%)*	*342 (95%)*	*57 (16%)*	233	28	35	170	32		109	22
Synthetic mesh	*2 (0%)*	*341 (80%)*	*6 (2%)*	*2 (0%)*	*341 (80%)*	*1 (0%)*	*6 (2%)*	1	209	5	1	132		0	1
Biological graft	*2 (0%)*	*5 (1%)*	*294 (81%)*	*0 (0%)*	*5 (1%)*	*2 (1%)*	*294 (81%)*	0	4	205	0	1		2	89
Mesh kit	*2 (0%)*	*1 (0%)*	*0 (0%)*	*2 (0%)*	*1 (0%)*	*0 (0%)*	*0 (0%)*	0	0	0	2	1		0	0
Other surgery	*19 (4%)*	*18 (4%)*	*6 (2%)*	*18 (4%)*	*18 (4%)*	*14 (4%)*	*6 (2%)*	13	9	6	5	9		1	0
No surgery	*8 (1%)*	*10 (2%)*	*5 (1%)*	*5 (1%)*	*10 (2%)*	*8 (2%)*	*5 (1%)*	5	5	4	0	5		3	1
Baseline questionnaire	*510 (94%)*	*414 (95%)*	*342 (93%)*	*409 (95%)*	*414 (95%)*	*340 (93%)*	*342 (93%)*	239	239	241	170	175		101	101
6-month questionnaire	*504 (94%)*	*381 (90%)*	*335 (92%)*	*398 (93%)*	*381 (88%)*	*338 (92%)*	*335 (91%)*	232	224	228	166	157		106	107
Withdrawals within 6 months	*0 (0%)*	*1 (0%)*	*1 (0%)*	*0 (0%)*	*1 (0%)*	*0 (0%)*	*1 (0%)*	0	1	1	0	0		0	0
Deaths within 6 months	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	0	0	0	0	0		0	0
12-month short questionnaire	*504 (94%)*	*389 (92%)*	*337 (93%)*	*395 (92%)*	*389 (89%)*	*342 (93%)*	*337 (92%)*	233	226	230	162	163		109	107
12-month long questionnaire	*468 (87%)*	*362 (85%)*	*316 (87%)*	*368 (86%)*	*362 (83%)*	*319 (87%)*	*316 (86%)*	219	212	214	149	150		100	102
12-month clinic assessment	*477 (89%)*	*374 (88%)*	*320 (88%)*	*381 (89%)*	*374 (86%)*	*319 (87%)*	*320 (87%)*	223	217	221	158	157		96	99
Withdrawals within 12 months	*2 (0%)*	*4 (1%)*	*2 (1%)*	*2 (0%)*	*4 (1%)*	*1 (0%)*	*2 (1%)*	1	4	2	1	0		0	0
Deaths within 12 months	*1 (0%)*	*0 (0%)*	*1 (0%)*	*1 (0%)*	*0 (0%)*	*0 (0%)*	*1 (0%)*	0	0	1	1	0		0	0
24-month questionnaire	*445 (82%)*	*343 (79%)*	*300 (82%)*	*348 (81%)*	*343 (79%)*	*299 (81%)*	*300 (82%)*	202	202	210	146	141		97	90
Withdrawals within 24 months	*13 (2%)*	*11 (3%)*	*5 (1%)*	*11 (3%)*	*11 (3%)*	*8 (2%)*	*5 (1%)*	6	8	4	5	3		2	1
Deaths within 24 months	*2 (0%)*	*0 (0%)*	*1 (0%)*	*1 (0%)*	*0 (0%)*	*1 (0%)*	*1 (0%)*	0	0	1	1	0		1	0

Type of repair	Secondary														
Stratum/comparison	All: 154			Trial 3: 107		Trial 4: 71		RCT3: 91			RCT2: 59			RCT2B: 4	
Treatment arm	Standard repair: 56	Synthetic mesh: 52	Mesh kit: 46	Standard repair: 55	Synthetic mesh: 52	Standard repair: 25	Mesh kit: 46	Standard repair: 24	Synthetic mesh: 24	Mesh kit: 43	Standard repair: 31	Synthetic mesh: 28		Standard repair: 1	Mesh kit: 3
Received surgery	*56 (100%)*	*51 (98%)*	*45 (98%)*	*55 (100%)*	*51 (98%)*	*25 (100%)*	*45 (98%)*	24	24	42	31	27		1	3
Standard repair	*49 (88%)*	*9 (18%)*	*4 (9%)*	*49 (89%)*	*9 (18%)*	*20 (80%)*	*4 (9%)*	20	3	3	29	6		0	1
Synthetic mesh	*3 (5%)*	*37 (73%)*	*7 (16%)*	*2 (4%)*	*37 (73%)*	*1 (4%)*	*7 (16%)*	0	17	7	2	20		1	0
Biological graft	*1 (2%)*	*0 (0%)*	*1 (2%)*	*1 (2%)*	*0 (0%)*	*1 (4%)*	*1 (2%)*	1	0	1	0	0		0	0
Mesh kit	*0 (0%)*	*2 (4%)*	*31 (69%)*	*0 (0%)*	*2 (4%)*	*0 (0%)*	*31 (69%)*	0	1	29	0	1		0	2
Other surgery	*3 (5%)*	*3 (6%)*	*2 (4%)*	*3 (5%)*	*3 (6%)*	*3 (12%)*	*2 (4%)*	3	3	2	0	0		0	0
No surgery	*0 (0%)*	*1 (2%)*	*1 (2%)*	*0 (0%)*	*1 (2%)*	*0 (0%)*	*1 (2%)*	0	0	1	0	1		0	0
Baseline questionnaire	*55 (98%)*	*50 (96%)*	*43 (93%)*	*54 (98%)*	*50 (96%)*	*24 (96%)*	*43 (93%)*	23	24	40	31	26		1	3
6-month questionnaire	*51 (91%)*	*47 (92%)*	*43 (96%)*		*47 (90%)*	*22 (88%)*	*43 (93%)*	21	23	41	29	24		1	2
Withdrawals within 6 months	*0 (0%)*	*0 (0%)*	*0 (0%)*		*0 (0%)*	*0 (0%)*	*0 (0%)*	0	0	0	0	0		0	0
Deaths within 6 months	*0 (0%)*	*0 (0%)*	*0 (0%)*		*0 (0%)*	*0 (0%)*	*0 (0%)*	0	0	0	0	0		0	0
12-month short questionnaire	*50 (89%)*	*44 (86%)*	*44 (98%)*	*49 (89%)*	*44 (85%)*	*21 (84%)*	*44 (96%)*	20	21	41	29	23		1	3
12-month long questionnaire	*47 (84%)*	*39 (76%)*	*41 (91%)*	*46 (84%)*	*39 (75%)*	*21 (84%)*	*41 (89%)*	20	17	39	26	22		1	2
12-month clinic assessment	*46 (82%)*	*44 (86%)*	*38 (84%)*	*46 (84%)*	*44 (85%)*	*21 (84%)*	*38 (83%)*	21	21	36	25	23		0	2
Withdrawals within 12 months	*1 (2%)*	*0 (0%)*	*0 (0%)*	*1 (2%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	0	0	0	1	0		0	0
Deaths within 12 months	*1 (2%)*	*0 (0%)*	*0 (0%)*	*1 (2%)*	*0 (0%)*	*1 (4%)*	*0 (0%)*	1	0	0	0	0		0	0
24-month questionnaire	*44 (79%)*	*39 (75%)*	*39 (85%)*	*43 (78%)*	*39 (75%)*	*20 (80%)*	*39 (85%)*	19	18	37	24	21		1	2
Withdrawals within 24 months	*1 (2%)*	*3 (6%)*	*2 (4%)*	*1 (2%)*	*3 (6%)*	*0 (0%)*	*2 (4%)*	0	3	2	1	0		0	0
Deaths within 24 months	*1 (2%)*	*0 (0%)*	*0 (0%)*	*1 (2%)*	*0 (0%)*	*1 (4%)*	*0 (0%)*	1	0	0	0	0		0	0

Type of repair	Primary: 1126	Secondary: 244	Uterine/vault: 215		
Stratum/comparison	Comprehensive cohort: 1585				
Treatment arm	CC1: 1126	CC2: 244	CC3: 215	Uterine: 69	Vault: 146
Received surgery	1104 (98%)	240 (98%)	212 (99%)	68 (99%)	144 (99%)
Standard repair	931 (84%)	128 (53%)	17 (8%)	12 (18%)	5 (3%)
Synthetic mesh	44 (4%)	52 (22%)	3 (1%)	0 (0%)	3 (2%)
Biological graft	45 (4%)	17 (7%)	0 (0%)	0 (0%)	0 (0%)
Mesh kit	17 (2%)	25 (10%)	1 (0%)	0 (0%)	1 (1%)
Other surgery	67 (6%)	18 (8%)	191 (90%)	56 (82%)	135 (94%)
No surgery	22 (2%)	4 (2%)	3 (1%)	1 (1%)	2 (1%)
Baseline questionnaire	997 (89%)	221 (91%)	202 (94%)	65 (94%)	137 (94%)
6-month questionnaire	966 (88%)	214 (89%)	175 (83%)	54 (79%)	121 (84%)
Withdrawals within 6 months	5 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (1%)
Deaths within 6 months	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (1%)
12-month short questionnaire	972 (88%)	216 (90%)	173 (82%)	57 (84%)	116 (81%)
12-month long questionnaire	893 (81%)	191 (80%)	158 (75%)	46 (68%)	112 (78%)
12-month clinic assessment	11 (1%)	8 (3%)	0 (0%)	0 (0%)	0 (0%)
Withdrawals within 12 months	14 (1%)	0 (0%)	5 (2%)	1 (1%)	4 (3%)
Deaths within 12 months	3 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (1%)
24-month questionnaire	848 (77%)	191 (80%)	152 (72%)	48 (71%)	104 (72%)
Withdrawals within 24 months	32 (3%)	6 (3%)	11 (5%)	3 (4%)	8 (6%)
Deaths within 24 months	3 (0%)	1 (0%)	4 (2%)	2 (3%)	2 (1%)

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